



(19)

Europäisches Patentamt  
European Patent Office  
Office européen des brevets



(11)

EP 1 243 268 A1

(12)

**EUROPEAN PATENT APPLICATION**  
published in accordance with Art. 158(3) EPC

(43) Date of publication:  
25.09.2002 Bulletin 2002/39

(51) Int Cl.7: **A61K 31/475, A61K 31/496,**  
**A61K 31/506, A61K 31/551,**  
**A61P 13/12**  
**// (C07D401/12, 401:14,**  
**409:14, 451:04, 491:056)**

(21) Application number: 00981658.8

(22) Date of filing: 13.12.2000

(86) International application number:  
**PCT/JP00/08782**

(87) International publication number:  
**WO 01/043746 (21.06.2001 Gazette 2001/25)**

(84) Designated Contracting States:  
AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU  
MC NL PT SE TR  
Designated Extension States:  
AL LT LV MK RO SI

(30) Priority: 14.12.1999 JP 35402299

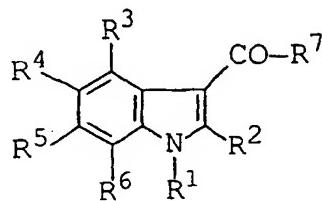
(71) Applicant: Nippon Shinyaku Co., Ltd.  
Kyoto-shi Kyoto 601-8550 (JP)

(72) Inventors:  
• TANIGUCHI, Norihisa  
Tsuchiura-shi, Ibaraki 300-0845 (JP)  
• SHIROUCHI, Yoshiaki  
Souraku-gun, Kyoto 619-0223 (JP)

(74) Representative: VOSSIUS & PARTNER  
Siebertstrasse 4  
81675 München (DE)

**(54) MEDICINAL COMPOSITION**

(57) The present invention is composed of a pharmaceutical composition for the therapy of nephritis which comprises an amide derivative represented by the following formula [1] or pharmaceutically acceptable salt thereof, as an active ingredient:



(1)

wherein R<sup>1</sup> and R<sup>2</sup> may be the same or different and each is hydrogen, alkyl which may be substituted, acyl, aryl which may be substituted, or an aromatic heterocyclic group which may be substituted; R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup> and R<sup>6</sup> may be the same or different and each is hydrogen, halogen, hydroxy, amino which may be substituted, alkyl which may be substituted, alkoxy or nitro and the like; and R<sup>7</sup> represents cyclic amino which may be substituted or azabicycloalkylamino which may be substituted.

The pharmaceutical composition of the invention is useful for the therapy of nephritis.

EP 1 243 268 A1

**Description****TECHNICAL FIELD**

- 5 [0001] The present invention relates to a composition for the therapy of nephritis which comprises an amide derivative or a pharmaceutically acceptable salt thereof as an active ingredient.

**BACKGROUND TECHNOLOGY**

10 [0002] According to the site of principal lesions, nephritis is classified into glomerulonephritis, interstitial nephritis and pyelonephritis, for instance. The most representative of all is glomerulonephritis in which the glomerular tuft is the affected site. Today, nephritis is synonymous with glomerulonephritis (Medical Dictionary, 1st ed., 570, 1987).

[0003] Histopathological findings which are most frequently obtained in human glomerulonephritis and considered to be of prognostic importance are mesangial cell proliferation and hyperplasia of the matrix produced by mesangial cells (hereinafter referred to as mesangial matrix). These findings are noted in nearly all types of proliferative glomerulonephritis, inclusive of IgA nephropathy, membranous proliferative glomerulonephritis, and lupus nephritis, in common (Iida: Kindney and Dialysis, 35, 505-509, 1993). And as the mesangial cell proliferation and associated production of mesangial matrix progress, the glomeruli fall into a terminal stage, so call glomerulosclerosis.

[0004] Therefore, any compound that inhibits mesangial cell proliferation and production of mesangial matrix is of great value as a therapeutic agent for glomerulonephritis.

[0005] At the same time, it is known that indole-3-carboxamide derivatives have an antagonistic action against serotonin and calmodulin, as well as herbicidal action, but they are not known to have mesangial cell growth inhibitory activity.

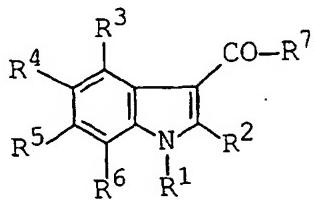
**DISCLOSURE OF THE INVENTION**

[0006] The objective of the present invention is to provide a novel pharmaceutical composition for the therapy of nephritis.

[0007] As a result of having conducted intensive studies on various compounds, the present inventors have found that an amide derivative of the present invention has mesangial cell growth inhibitory activity and is useful for the therapy of nephritis, and the present invention has been completed based on these findings.

[0008] Thus, the present invention is a pharmaceutical composition for the therapy of nephritis which comprises an amide derivative represented by the following formula [1] or a pharmaceutically acceptable salt thereof as an active ingredient:

35



45

[1]

wherein R<sup>1</sup> and R<sup>2</sup> may be the same or different and each is hydrogen, alkyl, haloalkyl, hydroxyalkyl, carboxyalkyl, acyl, aryl, aromatic heterocyclic group, or arylalkyl (the aryl moiety of the arylalkyl, the aryl and the aromatic heterocyclic group may be substituted by 1 to 3 same or different members selected from the group consisting of halogen, alkyl, haloalkyl, alkoxy, haloalkoxy, hydroxy, cyano, and nitro.);

R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup> and R<sup>6</sup> may be the same or different and each is hydrogen, halogen, hydroxy, amino, alkyl, haloalkyl, alkoxy, monoalkylamino, dialkylamino, arylalkyl, cyano or nitro. Or the two adjacent groups among R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup> and R<sup>6</sup> jointly represent methylenedioxy or ethylenedioxy;

R<sup>7</sup> represents cyclic amino which may be substituted by R<sup>8</sup>, or azabicycloalkylamino which may be substituted by R<sup>9</sup>;

R<sup>8</sup> represents alkyl, haloalkyl, acyl, aryl, aromatic heterocyclic group or arylalkyl (the aryl moiety of the arylalkyl, the aryl and the aromatic heterocyclic group may be substituted by 1 to 3 same or different members selected from

the group consisting of halogen, alkyl, arylalkyl, haloalkyl, alkoxy, hydroxy, amino, monoalkylamino, dialkylamino, alkylsulfonylamino, acylamino, dialkylaminosulfonylamino, carbamoyl, monoalkylcarbamoyl, dialkylcarbamoyl, cyano, carboxy, alkoxy carbonyl, alkylsulfonyl, dialkylaminosulfonyl and nitro.);

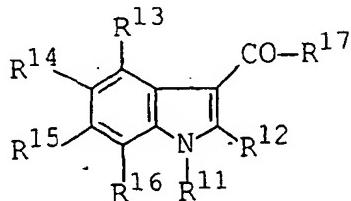
R<sup>9</sup> represents alkyl, alkenyl, (cycloalkyl)alkyl, haloalkyl, arylalkyl, acyl, alkylsulfonyl, or arylsulfonyl (the aryl moiety of the arylalkyl and the aryl moiety of the arylsulfonyl may be substituted by halogen or alkyl.).

[0009] It has not been known that the compounds represented by the above following formula [1] has mesangial cell growth inhibitory activity and is useful for the therapy of nephritis

[0010] The preferred compound among the compounds [1] of the present invention is an amide derivative represented by the following formula [1a] in either case of (A) or (B):

10

15



20

[1a]

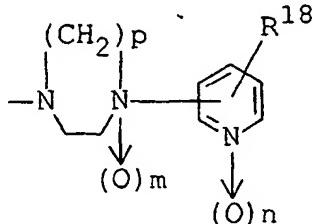
(A) wherein, R<sup>11</sup> and R<sup>12</sup> may be the same or different and each is alkyl, haloalkyl, hydroxyalkyl, carboxyalkyl, aryl, aromatic heterocyclic group, or arylalkyl (the aryl moiety of the arylalkyl, the aryl and the aromatic heterocyclic group may be substituted by 1 to 3 same or different members selected from the group consisting of halogen, alkyl, haloalkyl, alkoxy, haloalkoxy, hydroxy, cyano, and nitro.);

R<sup>13</sup>, R<sup>14</sup>, R<sup>15</sup> and R<sup>16</sup> may be the same or different and each is hydrogen, halogen, hydroxy, amino, alkyl, haloalkyl, alkoxy, monoalkylamino, dialkylamino, arylalkyl, cyano or nitro. Or the two adjacent groups among R<sup>13</sup>, R<sup>14</sup>, R<sup>15</sup> and R<sup>16</sup> may jointly form methylenedioxy or ethylenedioxy;

R<sup>17</sup> represents a group represented by the following formula [2]:

35

40



[2]

R<sup>18</sup> represents hydrogen, halogen, alkyl, arylalkyl, haloalkyl, alkoxy, hydroxy, amino, monoalkylamino, dialkylamino, alkylsulfonylamino, acylamino, dialkylaminosulfonylamino, carbamoyl, monoalkylcarbamoyl, dialkylcarbamoyl, cyano, carboxy, alkoxy carbonyl, alkylsulfonyl, dialkylaminosulfonyl, or nitro; m represents 0 or 1; n represents 0 or 1; and p represents 2 or 3.

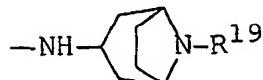
(B) wherein, R<sup>11</sup> represents hydrogen, alkyl, haloalkyl, hydroxyalkyl, carboxyalkyl, acyl, aryl, aromatic heterocyclic group or arylalkyl (the aryl moiety of the arylalkyl, the aryl and the aromatic heterocyclic group may be substituted by 1 to 3 same or different members selected from the group consisting of halogen, alkyl, haloalkyl, alkoxy, hydroxy, cyano and nitro.);

R<sup>12</sup> represents aryl or aromatic heterocyclic group (the aryl and the aromatic heterocyclic group may be substituted by 1 to 3 same or different members selected from the group consisting of halogen, alkyl, haloalkyl, alkoxy, hydroxy, cyano and nitro.);

R<sup>13</sup>, R<sup>14</sup>, R<sup>15</sup> and R<sup>16</sup> may be the same or different and each is hydrogen, halogen, hydroxy, amino, alkyl, haloalkyl, alkoxy, monoalkylamino, dialkylamino, arylalkyl, cyano or nitro. Or the two adjacent groups among R<sup>13</sup>, R<sup>14</sup>, R<sup>15</sup> and R<sup>16</sup> may jointly form methylenedioxy or ethylenedioxy;

R<sup>17</sup> represents a group represented by the following formula [3]:

5



[3]

10

R<sup>19</sup> represents hydrogen, alkyl, alkenyl, (cycloalkyl)alkyl, haloalkyl, arylalkyl, acyl, alkylsulfonyl, or arylsulfonyl (the aryl moiety of the arylalkyl and the aryl moiety of the arylsulfonyl may be substituted by halogen or alkyl.).

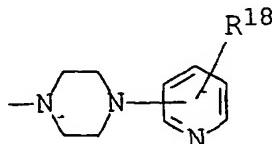
15

[0011] The preferred compound among the compounds [1a] of the present invention is the amide derivative wherein R<sup>11</sup> is alkyl and R<sup>12</sup> is phenyl (the phenyl may be substituted by 1 to 3 same or different members selected from the group consisting of halogen, alkyl, haloalkyl, alkoxy, haloalkoxy, hydroxy, cyano, and nitro) in either case (A) or (B).

[0012] The more preferred compounds among the compound [1a] of the present invention is the amide derivative wherein R<sup>11</sup> is alkyl and R<sup>12</sup> is phenyl, R<sup>13</sup>, R<sup>15</sup> and R<sup>16</sup> are respectively hydrogen, R<sup>14</sup> is hydrogen or alkyl, R<sup>17</sup> is a group represented by the following formula [2a]:

20

25



[2a]

30

R<sup>18</sup> is hydrogen or nitro in case (A).

[0013] The particularly preferred compounds among the compound [1a] of the present invention include, for example the following amide derivatives from (1) through (17):

35

- (1) 1-(1,5-Dimethyl-2-phenylindol-3-ylcarbonyl)-4-(2-pyridyl)piperazine
- (2) 1-(1,5-Dimethyl-2-phenylindol-3-ylcarbonyl)-4-(3-pyridyl)piperazine
- (3) 1-(1-Methyl-2-phenylindol-3-ylcarbonyl)-4-(5-nitro-2-pyridyl)-piperazine
- (4) 1-(1-Methyl-2-phenylindol-3-ylcarbonyl)-4-(2-pyridyl)piperazine-4-oxide
- (5) 1-(1,5,6-Trimethyl-2-phenylindol-3-ylcarbonyl)-4-(4-pyridyl)-piperazine
- (6) 1-(1-Methyl-2-phenylindol-3-ylcarbonyl)-4-(2-pyridyl)piperazine
- (7) 1-(1,5-Dimethyl-2-phenylindol-3-ylcarbonyl)-4-(4-pyridyl)piperazine
- (8) 1-(1,5-Dimethyl-2-phenylindol-3-ylcarbonyl)-4-(5-nitro-2-pyridyl)piperazine
- (9) 1-(1,5-Dimethyl-2-phenylindol-3-ylcarbonyl)-4-(2-pyridyl)-homopiperazine
- (10) 1-(1-Methyl-2-phenylindol-3-ylcarbonyl)-4-(3-pyridyl)-homopiperazine
- (11) 1-(1,5-Dimethyl-2-phenylindol-3-ylcarbonyl)-4-(3-pyridyl)homopiperazine
- (12) 1-(1,5-Dimethyl-2-phenylindol-3-ylcarbonyl)-4-(5-nitro-2-pyridyl)homopiperazine
- (13) 1-(1,5-Dimethyl-2-phenylindol-3-ylcarbonyl)-4-(5-methane-sulfonylamino-2-pyridyl)homopiperazine
- (14) 1-(1,5-Dimethyl-2-phenylindol-3-ylcarbonyl)-4-(5-acetylamino-2-pyridyl)homopiperazine
- (15) N-(endo-8-Methyl-8-azabicyclo[3.2.1]octa-3-yl)-1,5-dimethyl-2-phenylindole-3-carboxamide
- (16) N-(endo-8-Methyl-8-azabicyclo[3.2.1]octa-3-yl)-5-methoxy-1-methyl-2-phenylindole-3-carboxamide and
- (17) N-(endo-8-Methyl-8-azabicyclo[3.2.1]octa-3-yl)-1,6-dimethyl-2-phenylindole-3-carboxamide

50

55

[0014] In the present invention, "alkyl" includes straight or branched alkyl groups containing 1 to 7 carbons, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, isopentyl, n-hexyl, isohexyl, n-heptyl, and isoheptyl. Particularly, straight alkyl groups containing 1 to 3 carbons are preferred, and include, for example, methyl, ethyl and n-propyl. The alkyl moiety of "haloalkyl", "arylalkyl", "(cycloalkyl)alkyl", "alkoxy", "haloalkoxy", "monoalkylamino", "dialkylamino", "dialkylaminosulfonylamino" or "alkylsulfonyl" includes the above-mentioned alkyl.

[0015] The cycloalkyl moiety of "(cycloalkyl)alkyl" includes (cycloalkyl)alkyl group containing 3 to 7 carbons, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl.

[0016] "Alkenyl" includes straight or branched alkenyl groups containing 2 to 7 carbons, for example, allyl, 2-butene, 3-butene, 2-pentenyl, 3-pentenyl, 4-pentenyl, 4-methyl-3-pentenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 5-hexenyl, 2-heptenyl, 3-heptenyl, 4-heptenyl, 5-heptenyl and 6-heptenyl.

5 [0017] "Aryl" includes aryl groups containing 6 to 10 carbons, for example, phenyl, 1-naphthyl, and 2-naphthyl.

[0018] The aryl moiety of "arylalkyl" include the above-mentioned aryl.

10 [0019] "Azabicycloalkyl" includes azabicycloalkyl groups containing 3 to 8 carbons, for example, 2-azabicyclo[1.1.0]butyl, 1-azabicyclo[2.2.1] heptyl, 2-azabicyclo[2.2.1] heptyl, 7-azabicyclo[2.2.1] heptyl, 3-azabicyclo[3.1.1] heptyl, 2-azabicyclo[4.1.0] heptyl, 1-azabicyclo-[3.2.1] octyl, 8-azabicyclo[3.2.1] octyl, 1-azabicyclo[2.2.2] octyl, 2-azabicyclo[2.2.2] octyl, 4-azabicyclo[5.2.0] nonyl, and 9-azabicyclo-[3.3.1] nonyl.

15 [0020] "Aromatic heterocyclic group" includes 5- to 6-membered aromatic ring group having 1 to 4 heteroatoms selected from nitrogen, oxygen and sulfur. When atoms composing the ring of the aromatic heterocyclic group include nitrogen or sulfur atom, such nitrogen or sulfur atom may form oxide. For example, 1-pyrolyl, 2-pyrolyl, 3-pyrolyl, 2-furanyl, 3-furanyl, 2-thienyl, 3-thienyl, 2-oxazolyl, 2-thiazolyl, 2-imidazolyl, 4-imidazolyl, 1H-1,2,4-triazol-1-yl, 1H-tertazol-5-yl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyridine-1-oxid-2-yl, pyridine-1-oxid-3-yl, pyridine-1-oxid-4-yl, 2-pyrimidinyl, 4-pyrimidinyl, 2-pyradinyl and 1,3,5-triazin-2-yl are included.

[0021] "Halogen" includes, for example, fluorine, chlorine, bromine and iodine.

20 [0022] The halogen moiety of "haloalkyl" and "haloalkoxy" includes the above-mentioned halogen. "Haloalkyl" includes, for example, trifluoromethyl and 2,2,2-trifluoroethyl. "Haloalkoxy" includes, for example, trifluoromethoxy and 2,2,2-trifluoroethoxy.

[0023] "Acyl" includes acyl groups containing 1 to 11 carbons, for example, formyl, acetyl, propionyl, butyryl, isobutyryl, benzoyl, 1-naphthoyl, and 2-naphthoyl.

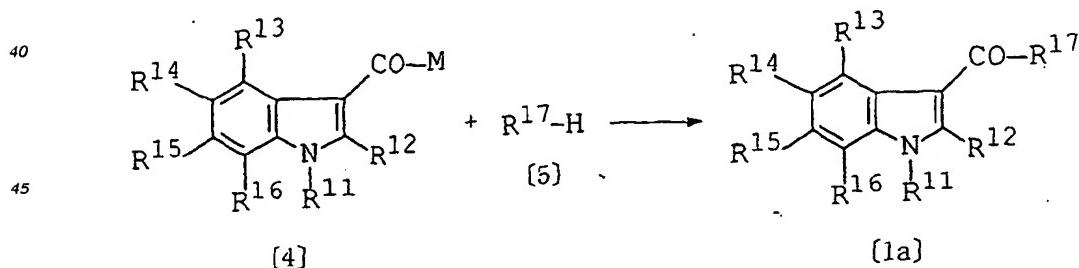
25 [0024] The acyl moiety of "acylamino" includes the above-mentioned acyl. For example, acetylamino, propionylamino, benzoylamino, 1-naphthoylamino and 2-naphthoylamino are included.

[0025] "Cyclic amino" may include 1 or 2 same or different members selected from the group consisting of nitrogen, oxygen and sulfur atoms as the atoms composing the ring. Four- to eight-membered ring groups are included. When atoms composing the ring of cyclic amino include nitrogen or sulfur atom, such nitrogen or sulfur atom may form oxide. For example, pyrrolidino, piperidino, piperazinyl, 3-methylpiperazin-1-yl, piperazine-4-oxid-1-yl, homopiperazinyl, morpholino, thiomorpholino, thiomorphorin-1,1-dioxid-4-yl, imidazol-1-yl, thiazolidin-3-yl are included.

30 [0026] The compound of the present invention represented by the above formula [1] can be produced by the methods described in WO97/26252, WO98/06715, BE901274A, GB2231265A or WO00/44743, or by the method described below.

[0027] The compound of the invention represented by the above formula [1a] can be produced, for example by the following.

35 [0028] The amide derivative [1a] can be produced by reacting the indole derivative [4] with amine [5]:



50 [wherein R<sub>11</sub>, R<sub>12</sub>, R<sub>13</sub>, R<sub>14</sub>, R<sub>15</sub>, R<sub>16</sub>, and R<sub>17</sub> are as defined previously. M represents a leaving group such as hydroxy, or halogen (chlorine, bromine, iodine, etc), alkoxy (e.g., methoxy), aryloxy (e.g., p-nitrophenoxy), alkylsulfoxyl (e.g., methanesulfoxyl), arylsulfoxyl (e.g., toluenesulfoxyl), imidazolyl, alkylcarboxyl or arylcarboxyl.]

55 [0029] Specifically, the amide derivative [1a] can be produced by the method in which the indole derivative [4] (where M is the above-mentioned leaving group other than hydroxy), for example, acid halide, alkyl ester, active ester, imidazolide or mixed acid anhydride is appropriately reacted with amine [5], or by the method in which the indole derivative [4] (where M is hydroxy) is directly bound to amine [5] using a condensing agent [for example, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide, dicyclohexylcarbodiimide, diisopropylcarbodiimide, benzotriazol-1-yl-tris(dimethylamino)phosphonium hexafluorophosphide salt, diphenylphosphorylazide or propane phosphate anhydride] in the presence

or absence of an additive (N-hydroxysuccinimide, 1-hydroxybenzotriazole, 3-hydroxy-4-oxo-3,4-dihydro-1,2,3-triazine, and the like).

[0030] When acid halide (the indole derivative [4] wherein M is halogen) is used, the amide derivative [1a] can be produced by reacting at -20 to 100°C in aprotic solvents (for example, polar solvents such as acetonitrile and N,N-dimethyl formamide (DMF), ether solvents such as tetrahydrofuran (THF) and diethyl ether, halogenated hydrocarbon solvents such as chloroform and methylene chloride, hydrocarbon solvents such as benzene, toluene and n-hexane, and the mixtures thereof) in the presence of a base (for example, potassium carbonate, sodium carbonate, sodium hydrogen carbonate, potassium hydrogen carbonate, pyridine, 4-dimethylaminopyridine, triethylamine, sodium hydride and the like). The reaction time is varied depending on the kinds of acid halide and amine [5] and the temperature of the reaction, and usually the appropriate reaction time is 30 min to 24 hours. The molar quantity of amine [5] for use is preferably 1 to 1.2 molar equivalents based on the acid halide.

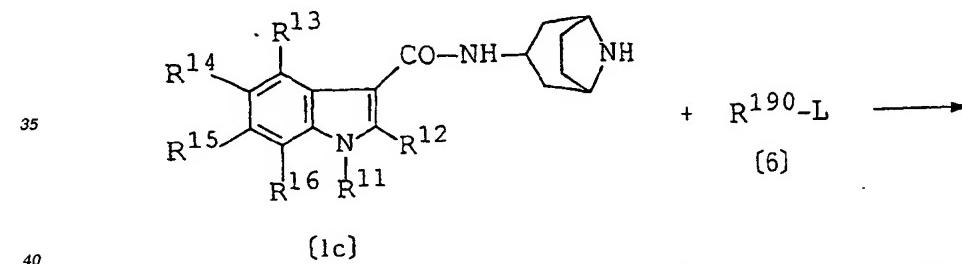
[0031] Such acid halide can be produced by reacting the indole derivative [4] (wherein M is hydroxy) and thionyl halide (e.g., thionyl chloride, thionyl bromide) at -20 to 100°C in the absence of a solvent or in the same aprotic solvent as the above-mentioned in the presence or absence of the same base as the above-mentioned. The reaction time is varied depending on the kind of acid halide and the temperature of the reaction, and usually the appropriate reaction time is 30 min to 24 hours. The amount of thionyl halide needed is equimolar or more equivalents based on the indole derivative [4], and an extremely excessive amount such as 10 molar equivalents or more can be used.

[0032] The indole derivative [4] (wherein M is hydroxy) and amine [5] used in this reaction as source materials are known compounds in the art, or can be produced according to the methods known in the art or by the methods represented in reference examples.

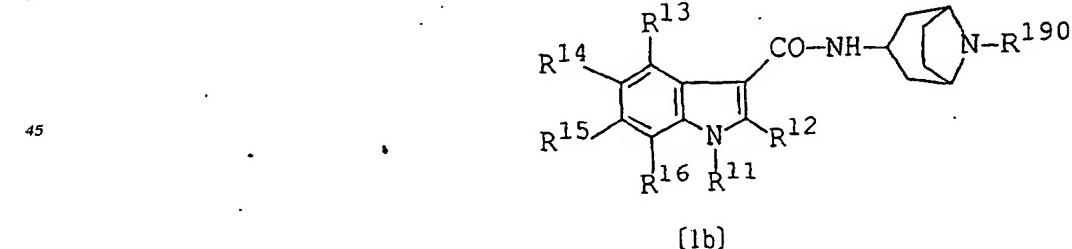
[0033] When a condensing agent is used, the amide derivative [1a] can be produced by reacting at -20 to 100°C in the same aprotic solvent as the above-mentioned in the presence or absence of the same base as the above-mentioned. The reaction time is varied depending on the kind of condensing agents and the temperature of the reaction, and usually the appropriate reaction time is 30 min to 24 hours. The amounts of amine [5] and a condensing agent for use are preferably 1 to 1.2 molar equivalents based on the indole derivative [4] (wherein M is hydroxy).

[0034] Among the compounds [1a] of the present invention, the compound [1b] wherein R<sup>17</sup> is the above-mentioned formula [3] and R<sup>19</sup> is a substituent other than hydrogen can also be produced by reacting the indole derivative [1c] with the compound [6]:

30



40



50

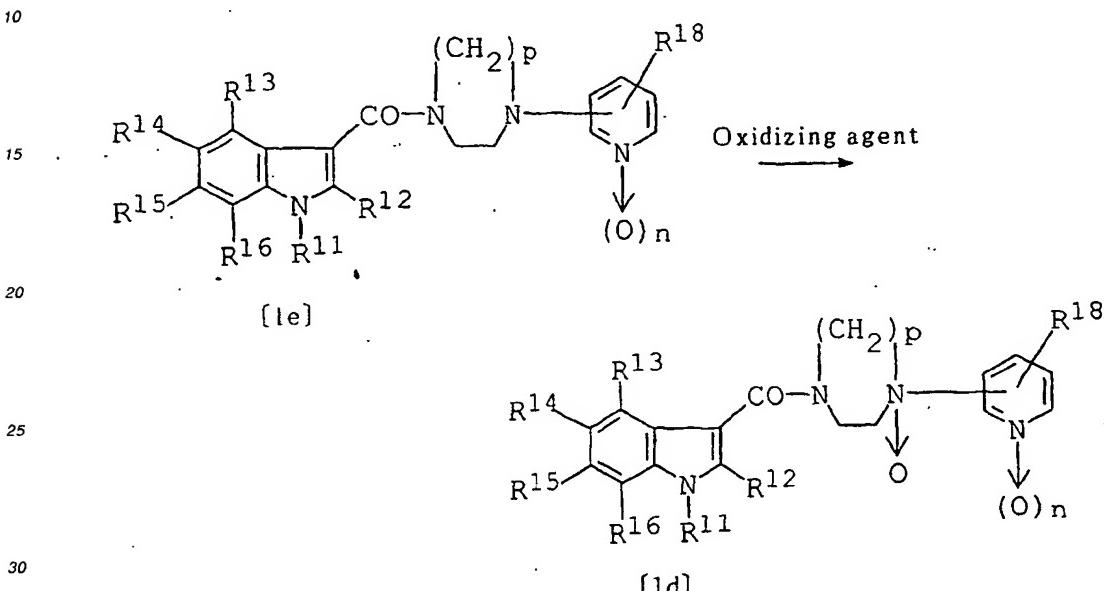
[wherein R<sup>11</sup>, R<sup>12</sup>, R<sup>13</sup>, R<sup>14</sup>, R<sup>15</sup>, and R<sup>16</sup> are as defined previously. R<sup>190</sup> represents R<sup>19</sup> other than hydrogen. L represents a leaving group such as halogen (e.g., chlorine, bromine, iodine), alkoxy (e.g., methoxy), aryloxy (e.g., p-nitrophenoxy), alkylsulfonyl (e.g., methanesulfonyl), arylsulfonyl (e.g., toluenesulfonyl), imidazolyl, alkylcarboxy or arylcarboxy.]

[0035] Specifically, the amide derivative [1b] can be produced by reaction at -20 to 100°C in protic solvents (alcoholic solvents such as methanol, ethanol and isopropanol) or in the above-mentioned aprotic solvents in the presence of the above-mentioned base. The reaction time is varied depending on the kind of the compound [6] and the temperature

of the reaction, and usually the appropriate reaction time is 30 min to 24 hours. The amount of the compound [6] for use is preferably 1 to 1.2 molar equivalents based on the amount of the indole derivative [1c].

[0036] The indole derivative [1c] used in this reaction as a source material can be produced in accordance with the process for producing the above amide derivative [1a].

[0037] Among the compounds [1a] of the present invention, the compound [1d] wherein R<sup>17</sup> is the above-mentioned formula [2] and m is 1 can also be produced by reacting the indole derivative [1e] with an oxidizing agent (organic peracids such as perbenzoic acid, m-chloro-perbenzoic acid and peracetic acid, or hydroperoxides such as tert-butyl hydroperoxide and tert-pentyl hydroperoxide):



[wherein R<sup>11</sup>, R<sup>12</sup>, R<sup>13</sup>, R<sup>14</sup>, R<sup>15</sup>, R<sup>16</sup>, R<sup>18</sup>, n and p are as defined previously.]

[0038] Specifically, the amide derivative [1d] can be produced by reacting at -50 to 70°C in the above-mentioned protic solvent or aprotic solvent. The reaction time is varied depending on the kind of the oxidizing agent and the temperature of the reaction, and usually the appropriate reaction time is 30 min to 24 hours. The amount of the oxidizing agent is preferably 1 to 1.2 molar equivalents based on the indole derivative [1e].

[0039] The indole derivative [1e] used in this reaction as a source material can be produced in accordance with the above process for producing amide derivative [1a].

[0040] In production of the above compound of the invention, it is common that the source materials are used for reaction after protecting with the protecting groups (for example, methoxymethyl, benzyl, 4-methoxybenzyl, 4,4'-dimethoxytrityl, acetyl, tert-butoxycarbonyl, benzyloxycarbonyl or phthaloyl) by the methods known in the art, when the source materials have substituents intended not to be reacted (for example, hydroxy, amino or carboxy). After the reaction, the protecting groups can be removed by the methods known in the art such as catalytic reduction, alkali treatment and acid treatment.

[0041] The compound of the invention can be isolated and purified from the above reaction mixture using the conventional means for isolation and purification such as extraction, concentration, neutralization, filtration, recrystallization, column chromatography or thin layer chromatography.

[0042] The compound of the invention can be used in the form of a free base as a medicine, however, it can be also used as a pharmaceutically acceptable salt made by the methods known in the art. These salts include salts of mineral acids such as hydrochloric acid, hydrobromic acid, sulfuric acid and phosphoric acid, and organic acids such as acetic acid, citric acid, tartaric acid, maleic acid, succinic acid, fumaric acid, p-toluenesulfonic acid, benzene sulfonic acid and methane sulfonic acid.

[0043] For example, hydrochloride of the amide derivative of the present invention can be obtained by dissolving the amide derivative in an alcohol or ether solution of hydrogen chloride.

[0044] As demonstrated in the test examples presented hereinafter, the compound of the present invention has excellent mesangial cell proliferation inhibitory activity. Moreover, its toxicological potential is low. Therefore, the pharmaceutical composition of the present invention is of value as a very desirable therapeutic drug for nephritis and is

effective in the treatment of chronic glomerulonephritis, especially proliferative glomerulonephritis, among various types of nephritis.

**[0045]** When the compound of the invention is administered as a medicine, it can be administered to mammals, including humans, either by itself or as a pharmaceutical composition in which the compound is contained in a pharmaceutically acceptable non-toxic and inert carrier in the proportion of, for example, 0.1 to 99.5%, or preferably 0.5 to 90%.

**[0046]** One or more auxiliary agents for formulation such as fillers or a solid, semisolid or liquid diluent are used. It is desirable to administer the pharmaceutical composition in unit dosage form. The pharmaceutical composition of the present invention can be administered intravenously, orally, topically (e.g., transdermally), rectally, or directly to the target tissue. The formulation suitable for these administration routes is specifically administered. Oral administration is preferable.

**[0047]** It is desirable to set the dosage of the compound for the therapy of nephritis by considering the condition of the patient, such as age, body weight, and the characteristics and severity of the disease and other factors such as the administration route; but usually for adults, an amount in the range of 0.1 to 1000 mg/person per day, and preferably 1 to 500 mg/ person per day, is generally a dose of the compound of the invention.

**[0048]** In some cases, amounts below this range are sufficient, and conversely, in other cases larger amounts are required. It can be administered by dividing the total dosage into two or three doses per day.

#### BEST MODE FOR CARRYING OUT THE INVENTION

**[0049]** The present invention is described in more detail by presenting Reference Examples, Preparation Examples, Test Examples and Formulation Examples of the compound of the invention, to which, however, the present invention is not limited.

##### Reference Example 1

###### N-Methyl-4-methylformanilide

**[0050]** p-Toluidine (51.2 g, 0.48 mol) and methyl orthoformate (76.5 g, 0.72 mol) was stirred with heat at 100°C for an hour in the presence of concentrated sulfuric acid (1.9g, 0.019mol) with distilling off by-producing methanol. The mixture was stirred at 175°C for another hour. Then the reaction mixture was distilled under reduced pressure to provide colorless oil (21.9 g).

Boiling point; 103-107°C /5 mmHg

##### Reference Example 2

###### N-Methyltoluidine

**[0051]** N-Methyl-4-methylformanilide (53.5 g, 0.36 mol) was refluxed in 163 ml of 10% hydrochloric acid solution for an hour. The reaction mixture was cooled and alkalized with an aqueous solution of 15% potassium hydroxide followed by being extracted with ether. The organic layer was washed with saturated brine, dried and concentrated. The resultant residue was distilled under reduced pressure to provide colorless oil (42.6 g).

Boiling point; 100-103°C /25 mmHg

##### Reference Example 3

###### N-Nitroso-N-methyltoluidine

**[0052]** N-Methyltoluidine (42.3 g, 0.35 mol) was added to a solution of concentrated hydrochloric acid (52 ml) and ice (142 g), and then 86 ml of an aqueous solution of sodium nitrite (24.1 g, 0.35 mol) was slowly added so that the reaction temperature did not exceed 10°C. The mixture was stirred for another one hour, then was extracted with ethyl acetate, washed with water, dried and concentrated. The resultant crude crystal was recrystallized from n-hexane to provide yellow crystal (47.9 g).

## Reference Example 4

1-Methyl-1-(4-methylphenyl)hydrazine

- 5 [0053] Zinc powder (85.3 g, 1.3 mol) was suspended in 142 ml of water, to which 90 ml of a solution of N-nitroso-N-methyltoluidine (47.8 g, 0.32 mol) in acetic acid was added dropwise over a period of 2.5 hours under ice cooling. The mixture was stirred for another 2.5 hours at room temperature. The reaction mixture was filtrated and the impurity was washed with 10% hydrochloric acid. The mother liquor was alkalized with an aqueous solution of 40% sodium hydroxide, and then was extracted with ether. The organic layer was washed with saturated brine, dried and concentrated. The residue was purified by column chromatography on silica gel (chloroform to chloroform : methanol = 50:1) to provide brown oil (33.3 g).
- 10

## Reference Example 5

15 Another process for producing 1-methyl-1-(4-methylphenyl)hydrazine

- [0054] Under argon atmospheric current, a solution of p-tolyl- hydrazine (6.38 g, 52.3 mmol) in dry tetrahydrofuran (20 ml) was added dropwise to a suspension of sodium amide (2.14 g, 54.9 mmol) in dry tetrahydrofuran (40 ml) for over 80 min under ice cooling. The reaction mixture was allowed to reach room temperature, and stirred for 30 min with bubbling argon gas to distill off ammonia. When the solution became almost homogenous brown, it was cooled down to 10 - 15°C again, and a solution of methyl iodine (7.79 g, 54.9 mmol) in dry tetrahydrofuran (20 ml) was added dropwise over a period of 80 min. The solution was stirred for 30 minutes as such, then ice was added to the reaction mixture. which was concentrated. The residue added water was extracted with ethyl acetate, dried and concentrated. The residuc was distilled under reduced pressure to provide the objective compound (4.1 g).

25 Boiling point: 61-63°C / 2 mmHg

The following compounds were produced as in the case with Reference Example 5.

- 1-Ethyl-1-phenylhydrazine  
1-Isopropyl-1-phenylhydrazine  
1-Benzyl-1-phenylhydrazine

30

## Reference Example 6

Ethyl 1,5-dimethyl-2-phenylindole-3-carboxylate

- 35 [0055] 1-Methyl-1-(4-methylphenyl)hydrazine (10.3 g, 76 mmol) and ethyl benzoylacetate (14.5 g, 76 mmol) were stirred in 40 ml of acetic acid at room temperature overnight. Ice-cold water and sodium hydrogen carbonate were added to the reaction mixture, which was extracted with ethyl acetate. The organic layer was washed with saturated brine, dried and concentrated. Polyphosphoric acid (100 g) was added to the residue, which was stirred for 30 min at 50-60°C. The reaction mixture was poured into ice-cold water and neutralized with an aqueous solution of 10% sodium hydroxide, then extracted with ethyl acetate. The organic layer was washed with saturated brine, dried and concentrated. The residue was purified by column chromatography on silica gel (chloroform) to provide pale yellow needles (6.15 g).

40

## Reference Example 7

45

1,5-Dimethyl-2-phenylindole-3-carboxylic acid

- [0056] Ethyl 1,5-dimethyl-2-phenylindole-3-carboxylate (6.15 g, 21 mmol), sodium hydroxide (8 g) and water (35 ml) were added to 80 ml of ethanol, and refluxed overnight. The reaction mixture was concentrated, to which 2N aqueous solution of sodium hydroxide was added, and was extracted with ethyl acetate. The aqueous phase was acidified with 6N hydrochloric acid, which was extracted with chloroform. The organic layer was washed with saturated brine, dried and concentrated. The residue was purified by column chromatography on silica gel (chloroform) to provide pale yellow crystal (5.06 g).

55

## Reference Example 8

1-(2-Fluoroethyl)-2-phenylindole

- 5 [0057] Sodium hydride (60%, 0.88 g) was suspended in 40 ml of dimethylsulfoxide, to which 2-phenylindole (3.86 g) was added under ice cooling. 1-Bromo-2-fluoroethane (2.79 g) was added dropwise to this mixture, and then stirred for 5 hours at room temperature and for an hour at 60°C. The reaction mixture was poured into ice-cold water, extracted with ethyl acetate, washed with water, dried and concentrated. The residue was purified by column chromatography on silica gel (n-hexane : ethyl acetate = 20:1) to provide pale yellow oil (4.33 g).

- 10 Reference Example 9

1-(2-Fluoroethyl)-2-phenyl-3-trifluoroacetylindole

- 15 [0058] Under argon atmospheric current, trifluoroacetic acid anhydride (4.56 g) was added dropwise to a solution of 1-(2-fluoroethyl)-2-phenylindole (4.33 g) in 20 ml of dimethylformamide at 0°C and stirred for an hour at the same temperature. Water was added to the reaction mixture, which was then extracted with ethyl acetate, then washed with water, dried and concentrated. The resultant crude crystal was washed with n-hexane and dried to provide the objective compound as iris powder (5.28 g).

20 Melting point: 130°C

## Reference Example 10

1-(2-Fluoroethyl)-2-phenylindole-3-carboxylic acid

- 25 [0059] 1-(2-Fluoroethyl)-2-phenyl-3-trifluoroacetylindole (5.28 g) and potassium hydroxide (4.42 g) were added to ethanol (50 ml)/water (17 ml), and refluxed for 2 hours. After cooling down, water was added to the reaction mixture, which was neutralized with diluted hydrochloric acid and extracted with ethyl acetate. The organic layer was washed with water, dried and concentrated. The resultant crude crystal was washed with ether and dried to provide pale yellow powder (3.65 g).

30 Melting point: 230°C

## Reference Example 11

Ethyl nicotinoylacetate

- 35 [0060] Diethyl carbonate (9.76 g) was added to a suspension of sodium hydride (60%, 4.96 g) in 30 ml of tetrahydrofuran, and refluxed for 10 min. A solution of 3-acetylpyridine (5.00 g) in 10 ml of tetrahydrofuran was added dropwise to this mixture over 30 min, and refluxed for 1.5 hours. After cooling down, the reaction mixture was poured into ice-cold water, which was neutralized with diluted hydrochloric acid and extracted with ethyl acetate, dried and concentrated. The residue was purified by column chromatography on silica gel (n-hexane : ethyl acetate = 2:1) to provide pale brown oil (4.11 g).

The following compounds were produced as in the case with Reference Example 11.

Ethyl isonicotinoylacetate

- 40 45 Ethyl 2-naphthoylacetate

Ethyl (4-methoxybenzoyl)acetate

Ethyl (3-methoxybenzoyl)acetate

Ethyl (4-methylbenzoyl)acetate

Ethyl (4-nitrobenzoyl)acetate

- 50 55 Ethyl (4-chlorobenzoyl)acetate

Ethyl (4-fluorobenzoyl)acetate

Ethyl (4-hydroxybenzoyl)acetate

Ethyl (3-trifluoromethylbenzoyl)acetate

Ethyl 2-thiophencarbonylacetate

- 55 [0061] The following compounds were produced as in the case with Reference Examples 6 and 7 using the above ethyl acetate derivatives.

1-Methyl-2-(3-pyridyl)indole-3-carboxylic acid

1-Methyl-2-(4-pyridyl)indole-3-carboxylic acid

- 1-Methyl-2-(2-naphthyl)indole-3-carboxylic acid  
 1-Methyl-2-(3-methoxyphenyl)indole-3-carboxylic acid  
 1-Methyl-2-(4-methoxyphenyl)indole-3-carboxylic acid  
 1,5-Dimethyl-2-(4-methylphenyl)indole-3-carboxylic acid  
 5 1,5-Dimethyl-2-(4-nitrophenyl)indole-3-carboxylic acid  
 1-Methyl-2-(4-chlorophenyl)indole-3-carboxylic acid  
 1-Methyl-2-(4-fluorophenyl)indole-3-carboxylic acid  
 1-Methyl-2-(4-hydroxyphenyl)indole-3-carboxylic acid  
 1-Methyl-2-(3-trifluoromethyl)indole-3-carboxylic acid  
 10 1-Methyl-2-(thienyl)indole-3-carboxylic acid

## Reference Example 12

endo-8-Methyl-8-azabicyclo[3.2.1]octan-3-amine

[0062] Hydroxylaminé hydrochloride (6.0 g) and sodium acetate (7.2 g) were dissolved in 50 ml of methanol, and stirred for an hour. Tropanone (10.0 g) was added and stirred for 5 hours. The reaction mixture was concentrated and water was added to the residue, which was alkalized with potassium carbonate, and then extracted with chloroform, washed with saturated brine, dried and concentrated. The resultant crude crystals were washed with n-hexane to provide endo-8-methyl-8-azabicyclo[3.2.1] octan-3-one oxime (10.0 g).

[0063] Lithium aluminium hydride (4.5 g) was suspended in 80 ml of dry tetrahydrofuran, to which a solution of concentrated sulfuric acid (5.8 g) in 15 ml of dry tetrahydrofuran was added at -10 to -20°C over about 30 minutes. The mixture was further stirred for 3 hours. Then, a solution of endo-8-methyl-8-azabicyclo[3.2.1] octan-3-one oxime (5.0 g) in 75 ml of dry tetrahydrofuran was added dropwise over to this mixture, and stirred at 40°C for 1.5 hours. The reaction mixture was cooled down, to which wet ether was added. The precipitated inorganic salts were removed through Celite filtration, and the ether phase was fractionated, dried and concentrated to provide the objective compound as brown oil (2.0 g).

## Reference Example 13

8-Benzyl-8-azabicyclo[3.2.1] octan-3-one

[0064] 2,5-Dimethoxy tetrahydrofuran (25 g) was added to 227 ml of 0.1N hydrochloric acid, and stirred with heat at 80°C for an hour. The mixture was cooled to 10°C, to which acetone dicarboxylic acid (30.39 g), sodium acetate (18.61 g) and concentrated sulfuric acid (17.4 ml) were added and stirred. Further, benzylamine (22.28 g) was added dropwise to the resultant mixture, and stirred overnight at room temperature. The reaction mixture was alkalized with aqueous solution of sodium hydroxide, and then was extracted with chloroform. The organic layer was washed with water, dried and concentrated to provide the objective compound as brown oil (41.4 g).

## Reference Example 14

8-Benzyl-8-azabicyclo[3.2.1] octan-3-one oxime

[0065] Hydroxylamine hydrochloride (3.87 g) and sodium acetate (4.57 g) were added to 50 ml of methanol, and stirred for 30 min. Then, 8-benzyl-8-azabicyclo[3.2.1] octan-3-one (10 g) was added and stirred for 5 hours. The reaction mixture was concentrated, alkalized with potassium carbonate and water and then extracted with chloroform. The organic layer was washed with saturated brine, dried and concentrated. The resultant crude crystals were washed with n-hexane to provide white crystals (7.8 g).

## Reference Example 15

8-Benzyl-8-azabicyclo[3.2.1] octan-3-amine

[0066] Under argon atmospheric current, a solution of concentrated sulfuric acid (22.02 g) in 50 ml of tetrahydrofuran was slowly added dropwise to a suspension of lithium aluminium hydride (17.04 g) in 250 ml of tetrahydrofuran at -20°C. The mixture was allowed to reach room temperature, and then stirred for an hour. Then, a solution of 8-benzyl-8-azabicyclo[3.2.1] octan-3-one oxime (25.85 g) in 200 ml of tetrahydrofuran was added dropwise over a period of an hour, and stirred at room temperature for another one hour. Wet ether was added to the reaction mixture to quench,

and then filtrated through Celite. The mother liquor was concentrated to provide orange oil (20.4 g).

Reference Example 16

5    8-Benzyl-3-(tert-butoxycarbonylamino)-8-azabicyclo [3.2.1]octane

[0067] 8-Benzyl-8-azabicyclo[3.2.1] octan-3-amine (20.4 g) was dissolved in 200 ml of chloroform, to which triethylamine (9.57 g) was added. A solution of di-tert-butyl dicarbonate (20.58 g) in 50 ml of chloroform was added dropwise to this mixture, and stirred at room temperature for 16 hours. The reaction mixture was concentrated. The residue was purified by column chromatography on silica gel (chloroform : methanol = 5:1) to provide white crystals (18.14 g).

Reference Example 17

15    3-(tert-Butoxycarbonylamino)-8-azabicyclo[3.2.1]octane

[0068] 8-Benzyl-3-(tert-butoxycarbonylamino)-8-azabicyclo [3.2.1]octane was dissolved in 400 ml of methanol followed by adding formic acid (25.80 g) and 10% palladium carbon (5 g). The mixture was stirred at room temperature for 16 hours. Then, the catalyst was removed by filtration. The mother liquor was alkalized by adding an aqueous solution of sodium hydroxide, which was extracted with chloroform. The organic layer was dried and concentrated. The residue was purified by column chromatography on silica gel (chloroform : methanol = 5:1) to provide brown oil (12 g).

Reference Example 18

25    8-Benzoyloxycarbonyl-3-(tert-butoxycarbonylamino)-8-azabicyclo[3.2.1]octane

[0069] 3-(tert-Butoxycarbonylamino)-8-azabicyclo[3.2.1] octane (12 g) and triethylamine (5.93 g) were dissolved in 100 ml of methylene chloride, to which benzylchloroformate (9.99 g) was added dropwise under ice cooling. After stirring for 16 hours at room temperature, an aqueous saturated solution of sodium hydrogen carbonate was added to the reaction mixture, which was extracted with chloroform. The organic layer was dried and concentrated. The residue was purified by column chromatography on silica gel (chloroform) to provide colorless oil (17 g).

Reference Example 19

35    endo-8-Benzoyloxycarbonyl-8-azabicyclo[3.2.1] octan-3-amine

[0070] 8-Benzoyloxycarbonyl-3-(tert-butoxycarbonylamino)-8-azabicyclo[3.2.1] octane (17 g) was dissolved in 50 ml of methylene chloride, to which 50 ml of trifluoroacetic acid was added dropwise under ice cooling. After stirring at room temperature for 3 hours, an aqueous solution of sodium hydroxide was added to the reaction mixture, which was extracted with chloroform. The organic layer was dried and concentrated. The residue was separated and purified by column chromatography on silica gel (chloroform : methanol = 15:1) to provide only endo-substance as faint yellow oil (7.2 g).

Reference Example 20

45    1-(5-Nitro-2-pyridyl)homopiperazine

[0071] Homopiperazine (6.01 g, 0.06 mol) was dissolved in 30 ml of toluene, to which 2-chloro-5-nitropyridine was added in several small portions under ice cooling. Further, 50 ml of toluene was added and stirred at room temperature for 15 min. The reaction mixture was partitioned by adding ethyl acetate and 2N-sodium hydroxide. The organic layer was washed with saturated brine, dried and concentrated. The resultant crude crystals were washed with isopropyl ether to provide yellow crystals (4.03 g).

[0072] The following compound was produced by heating at 100°C for 5 hours as in the case with Reference Example 20.

55    1-(5-Carbomethoxy-2-pyridyl)homopiperazine

## Reference Example 21

1-Benzoyloxycarbonyl-4-(5-nitro-2-pyridyl)homopiperazine

5 [0073] 1-(5-Nitro-2-pyridyl)homopiperazine (3.00 g, 13.5 mmol) was dissolved in 50 ml of methylene chloride, to which triethylamine (4.10 g, 40.6 mmol) was added. Then, benzylchloroformate (30-35% toluene solution) (9.20 g) was added dropwise under ice cooling, and stirred at 0°C for an hour and at room temperature for 2 hours. Water was added to the reaction mixture, which was extracted with chloroform. The organic layer was dried and concentrated. The resultant residue was purified by column chromatography on silica gel (n-hexane : ethyl acetate = 2:3) to provide 10 the objective compound (3.43 g).

## Reference Example 22

1-Benzoyloxycarbonyl-4-(5-amino-2-pyridyl)homopiperazine

15 [0074] 1-Benzoyloxycarbonyl-4-(5-nitro-2-pyridyl)homopiperazine (2.15 g) was dissolved in 20 ml of concentrated hydrochloric acid and 10 ml of ethanol, to which 10 ml of an aqueous solution of tin chloride (II) dihydrate (6.81 g) was slowly added dropwise under ice cooling. The mixture was stirred at 0°C for 30 min and at room temperature for an hour. The reaction mixture was neutralized with an aqueous solution of sodium hydroxide, and the resultant precipitate 20 was filtrated through Celite. The filtrate was extracted with chloroform. The organic layer was dried and concentrated to provide purple oil (2.06 g).

## Reference Example 23

1-(5-Dimethylamino-2-pyridyl)homopiperazine

25 [0075] 1-Benzoyloxycarbonyl-4-(5-amino-2-pyridyl)homopiperazine (1.47 g) was dissolved in 1% acetic acid / methanol (30 ml), to which 37% formalin was added, and stirred at room temperature for an hour. Then, sodium cyanoborohydride (1.70 g) was added, and stirred at room temperature for 1.5 hours. Under ice cooling, an aqueous solution 30 of sodium hydrogen carbonate was added to the reaction mixture, and methanol was distilled off under reduced pressure. The residue was extracted with chloroform, dried and concentrated. The residue was purified by column chromatography on silica gel (n-hexane : ethyl acetate = 1:1) to provide yellow oil (1.45 g). This was deprotected by hydrogenation with 10% palladium carbon to provide the objective compound (0.80 g).

## 35 Reference Example 24

1-(5-Methanesulfonamino-2-pyridyl)homopiperazine

40 [0076] 1-Benzoyloxycarbonyl-4-(5-amino-2-pyridyl)homopiperazine (500 mg) was dissolved in 15 ml of methylene chloride, to which triethylamine (209 mg) was added. A solution of methanesulfonyl chloride (210 mg) in 5 ml of methylene chloride was added dropwise under ice cooling and stirred for 3 hours. Water was added to the reaction mixture, which was extracted with chloroform, dried and concentrated. The resultant residue was purified by column chromatography on silica gel (chloroform : methanol = 50:1) to provide oil (469 mg). This was deprotected by hydrogenation with 10% palladium carbon to provide the objective compound (539 mg).

45 [0077] The following compounds were produced as in the case with Reference Example 24.

- 1-(5-Methanesulfonamino-2-pyridyl)piperazine
- 1-(5-Dimethylsulfamoylamino-2-pyridyl)piperazine
- 1-(5-Acetylamino-2-pyridyl)homopiperazine
- 1-(5-Dimethylsulfamoylamino-2-pyridyl)homopiperazine

50

## Reference Example 25

1-(2-Pyridyl)homopiperazine

55 [0078] Under argon atmospheric current, 2-bromopyridine (20.0 g, 0.13 mol) was dissolved in 200 ml of toluene, to which homopiperazine (76.32 g, 0.76 mol), palladium acetate (II) (29 mg, 0.13 mmol), tri(t-butyl)phosphine (103 mg, 0.51 mmol), and sodium t-butoxide (16.65 g, 0.17 mol) were successively added, and then stirred with heat at 120°C overnight. The reaction mixture was poured into ice-cold water, which was extracted with chloroform five times. The

**EP 1 243 268 A1**

organic layer was dried and concentrated. The resultant residue was distilled under reduced pressure to provide the objective compound as yellow oil (17.28 g).

Boiling point: 125-130°C/ 8 mmHg

[0079] The following compounds were produced as in the case with Reference Example 25.

- 5    1-(3-Pyridyl)piperazine  
    1-(4-Pyridyl)piperazine  
    1-(3-Pyridyl)homopiperazine

Reference Example 26

- 10    1-(2-Pyridyl)-4-trifluoroacetyl homopiperazine

[0080] 1-(2-Pyridyl)homopiperazine (0.50 g) was dissolved in 10 ml of methanol, to which ethyl trifluoroacetate (0.48 g) and triethylamine (0.34 g) was added, and stirred at room temperature overnight. Then, chloroform was added to the reaction mixture, which was washed with saturated brine. The organic layer was dried and concentrated to provide colorless oil (0.77 g).

Reference Example 27

- 20    2-(4-Trifluoroacetyl homopiperazin-1-yl) pyridin-5-sulfonyl chloride

[0081] 1-(2-Pyridyl)-4-trifluoroacetyl homopiperazine (0.77 g) was dissolved in 3 ml of chloroform, to which chlorosulfonic acid (1.32 g) was added, and refluxed overnight. Saturated aqueous solution of sodium bicarbonate was added to the reaction mixture, which was extracted with chloroform. The organic layer was dried and concentrated to provide brown crystals (0.46 g).

Reference Example 28

- 30    N,N-Diethyl 2-(4-trifluoroacetyl homopiperazin-1-yl) pyridin-5-sulfonamide

[0082] 2-(4-Trifluoroacetyl homopiperazin-1-yl) pyridin-5-sulfonylchloride (0.25 g) was dissolved in 5 ml of methylene chloride, to which diethylamine (0.10 g) was added, and stirred at room temperature for 2 hours. The reaction mixture was washed with water, dried and concentrated. The resultant residue was purified by column chromatography on silica gel (chloroform) to provide brown crystals (0.21 g).

35    Reference Example 29

- 40    N,N-Diethyl 2-(homopiperazin-1-yl) pyridin-5-sulfonamide

[0083] N,N-Diethyl 2-(4-trifluoroacetyl homopiperazin-1-yl)pyridin-5-sulfonamide (0.21 g) was dissolved in methanol, to which sodium carbonate (0.27 g) dissolved in 3 ml of water was added, and stirred at room temperature overnight. Chloroform was added to the reaction mixture, which was then washed with saturated aqueous solution of sodium bicarbonate and saturated brine. The organic layer was dried and concentrated to provide brown oil (0.14 g).

45    Reference Example 30

- 50    2-Chloro-5-benzyloxy pyridine

[0084] 2-Chloro-5-hydroxy pyridine (300 mg) was dissolved in 20 ml of dimethylformamide, to which potassium carbonate (476 mg) and benzyl chloride (472 mg) were added, and stirred with heat at 75°C for 3 hours. Water was added to the reaction mixture, which was extracted with chloroform. The organic layer was dried and concentrated. The resultant residue was purified by column chromatography on silica gel (chloroform) to provide pale yellow oil (527 mg).

55    Reference Example 31

- 55    1-(5-Hydroxy-2-pyridyl)piperazine

[0085] Under argon atmospheric current, piperazine (1.19 g), tris-(dibenzylidene acetone) dipalladium (0) (37 mg),

1,3-bis (diphenylphosphino) propane (38 mg), and sodium t-butoxide (313 mg) were successively added to a solution of 2-chloro-5-benzylxy pyridine (520 mg) in 10 ml of toluene, and stirred with heat at 90°C overnight. Water was added to the reaction mixture, which was extracted with ethyl acetate, dried and concentrated. The resultant residue was purified by column chromatography on silica gel (chloroform : methanol : ammonia = 30:1:0.1) to provide brown oil (498 mg). This was hydrogenated with 10% palladium carbon at normal pressures and room temperature to provide the objective compound as colorless oil (248 mg).

## Preparation Example 1

10 1-(1,5-Dimethyl-2-phenylindol-3-ylcarbonyl)-4-(2-pyridyl)piperazine hydrochloride

[0086] 1,5-Dimethyl-2-phenylindole-3-carboxylic acid (3.00 g) was dissolved in 30 ml of dimethylformamide, to which 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (hereinafter referred to as WSCD/HCl) (2.38 g) and 1-hydroxy benzotriazole (1.68 g) were added, and stirred for 30 min. Then, 1-(2-pyridyl)piperazine (2.00 g) was added, and stirred overnight. The reaction mixture was poured into water and extracted, with ethyl acetate, dried and concentrated. The residue was purified by column chromatography on silica gel (n-hexane : ethyl acetate = 2:1) to provide white crystals. These crystals were dissolved in methanol, and 1M hydrogen chloride/ether (9 ml) was added to the solution, and then the solution was concentrated under reduced pressure to be dried.

The objective compound was obtained as amorphous (4.2 g)

20

Elemental analysis for C <sub>26</sub> H <sub>26</sub> N <sub>4</sub> O·HCl·H <sub>2</sub> O			
Calculated (%)	C:67.16	H: 6.29	N:12.05
Found (%)	C:67.19	H: 6.15	N:12.05

25

## Preparation Example 2

1-[1-(2-Fluoroethyl)-2-phenylindol-3-ylcarbonyl]-4-(2-pyridyl)piperazine hydrochloride

[0087] 1-(2-Fluoroethyl)-2-phenylindole-3-carboxylic acid (1.13 g) was dissolved in 30 ml of dimethylformamide, to which WSCD/HCl (0.92 g) and 1-hydroxy benzotriazole (0.65 g) were added, and stirred for an hour. Then, 1-(2-pyridyl)piperazine (0.78 g) was added and stirred overnight. The reaction mixture was concentrated, to which water was added. Then, it was extracted with ethyl acetate, dried and concentrated. The residue was purified by column chromatography on silica gel (n-hexane : ethyl acetate = 3:1) to provide colorless amorphous. This was dissolved in methanol, and 1M hydrogen chloride / ether (3 ml) was added to the solution, and then the solution was concentrated under reduced pressure to be dried. The objective compound was obtained as pale yellow powder (1.13 g).

Melting point: 131°C

40

Elemental analysis for C <sub>26</sub> H <sub>25</sub> FN <sub>4</sub> O·HCl·2H <sub>2</sub> O			
Calculated (%)	C:62.33	H: 6.04	N:11.18
Found (%)	C:62.73	H: 6.21	N:11.91

## Preparation Example 3

45

endo-(8-Azabicyclo[3.2.1]octa-3-yl)-1-methyl-2-phenylindole-3-carboxamide hydrochloride

## Step 1

50

endo-(8-Benzylloxycarbonyl-8-azabicyclo[3.2.1] octa-3-yl)-1-methyl-2-phenylindole-3-carboxamide

55

[0088] 1-Methyl-2-phenylindole-3-carboxylic acid (3.16 g) was dissolved in 80 ml of dimethylformamide, to which WSCD/HCl (2.65 g) and 1-hydroxy benzotriazole (1.87 g) were added, and stirred for 30 min. Then, endo(8-benzylloxycarbonyl-8-azabicyclo[3.2.1]octane-3-amine (3.6 g) was added, and stirred overnight. The reaction mixture was poured into water, and was extracted with chloroform, and dried and concentrated. The resultant crude crystals were washed with n-hexane to provide white crystals (5.8 g).

## Step 2

N-(endo-8-Azabicyclo[3.2.1]octa-3-yl)-1-methyl-2-phenylindole-3-carboxamide hydrochloride

- 5 [0089] endo-(8-Benzylloxycarbonyl-8-azabicyclo[3.2.1] octa-3-yl)-1-methyl-2-phenylindole-3-carboxamide (5.8 g) was dissolved in a mixed solvent of ethanol (200 ml) and methylene chloride (50 ml), which was hydrogenated with 10% palladium carbon (5g) at atmospheric pressures for 10 hours. The reaction mixture was filtrated to eliminate the catalyst. The mother liquor was concentrated. The resultant crude crystals were washed with ether to provide white crystals (3.4 g), of which 200 mg was converted to hydrochloride with hydrogen chloride/ether to provide the objective compound (150 mg).
- 10 Melting point: 298°C  
EI-MS m/z: 359[M]+

## Preparation Example 4

endo-(8-Allyl-8-azabicyclo[3.2.1]octa-3-yl)-1-methyl-2-phenylindole-3-carboxamide hydrochloride

- 15 [0090] endo-(8-Azabicyclo[3.2.1]octa-3-yl)-1-methyl-2-phenylindole-3-carboxamide (200 mg) was dissolved in 5 ml of ethanol, to which potassium carbonate (384 mg) and allyl bromide (74 mg) was added, and stirred with heat at 60°C for 2 hours. The reaction mixture was filtrated. Saturated aqueous solution of sodium hydrogen carbonate was added to the mother liquor, and extracted with chloroform. The organic layer was dried and concentrated. The residue was purified by column chromatography (chloroform : methanol = 10:1). The resultant colorless oil was converted to hydrochloride with hydrogen chloride/ether to provide the objective compound (130 mg).

20 Melting point: 155°C  
25 EI-MS m/z: 399[M]+

## Preparation Example 5

1-(1-Methyl-2-phenylindol-3-ylcarbonyl)-4-(2-pyridyl)piperazine-4-oxide

- 30 [0091] 1-(1-Methyl-2-phenylindol-3-ylcarbonyl)-4-(2-pyridyl)piperazine (2.38 g) was dissolved in 12 ml of methylene chloride. Under ice cooling, m-chloroperbenzoic acid (1.24 g) was added and stirred for an hour. Then, it was allowed to reach room temperature and stirred overnight. Water was added to the reaction mixture, and was extracted with methylene chloride, and washed with water, dried and concentrated. The residue was purified by column chromatography on silica gel (chloroform : methanol = 20:1) to provide pale brown amorphous. It was recrystallized from ethyl acetate to provide the objective compound as pale yellow powder (1.75 g).

35 Melting point: 152°C

Elemental analysis for C <sub>25</sub> H <sub>24</sub> N <sub>4</sub> O <sub>2</sub> ·1.5H <sub>2</sub> O			
Calculated (%)	C:68.32	H: 6.19	N:12.75
Found (%)	C:67.97	H: 6.22	N:12.51

40 [0092] The following compounds in Preparation Examples 6 through 42, 44 through 53, 55 through 83, 86 through 91, 93, 95 through 102, 107 through 110, and 115 through 184 were produced as in the case with Preparation Example 1.

45 [0093] The following compounds in Preparation Examples 92, and 111 through 114 were produced as in the case with Preparation Example 3.

[0094] The following compounds in Preparation Examples 84 and 85, 94, 103 and 104, and 105 and 106 were produced as in the case with Preparation Example 4.

50 [0095] The following compounds in Preparation Examples 43 and 54 were produced as in the case with Preparation Example 5.

## Preparation Example 6

1-(1-Methyl-2-phenylindol-3-ylcarbonyl)-4-(2-pyridyl)piperazine hydrochloride

55 [0096] Melting point: 171-172°C

5

Elemental analysis for C <sub>25</sub> H <sub>24</sub> N <sub>4</sub> O·HCl·1.5H <sub>2</sub> O			
Calculated (%)	C:65.28	H: 6.14	N:12.18
Found (%)	C:65.23	H: 5.92	N:12.12

## Preparation Example 7

1-(5-Chloro-1-methyl-2-phenylindol-3-ylcarbonyl)-4-(2-pyridyl) piperazine hydrochloride

10

[0097] Melting point: 236°C

15

Elemental analysis for C <sub>25</sub> H <sub>23</sub> ClN <sub>4</sub> O·HCl·0.75H <sub>2</sub> O			
Calculated (%)	C:62.44	H: 5.34	N:11.65
Found (%)	C:62.43	H: 5.30	N:11.52

## Preparation Example 8

20

1-[1-Methyl-2-(4-fluorophenyl)indol-3-ylcarbonyl-4-(2-pyridyl)piperazine hydrochloride

[0098] Melting point: 222°C

25

Elemental analysis for C <sub>25</sub> H <sub>23</sub> FN <sub>4</sub> O·HCl·H <sub>2</sub> O			
Calculated (%)	C:64.03	H: 5.59	N:11.95
Found (%)	C:64.40	H: 5.64	N:11.83

## Preparation Example 9

30

1-(6-Fluoro-1-methyl-2-phenylindol-3-ylcarbonyl)-4-(2-pyridyl)piperazine dihydrochloride

[0099] Melting point: 256°C

35

Elemental analysis for C <sub>25</sub> H <sub>23</sub> FN <sub>4</sub> O·2HCl·0.5H <sub>2</sub> O			
Calculated (%)	C:60.49	H: 5.28	N:11.29
Found (%)	C:60.26	H: 5.38	N:11.02

40

## Preparation Example 10

1-(5-Methoxy-1-methyl-2-phenylindol-3-ylcarbonyl)-4-(2-pyridyl)piperazine hydrochloride

45

[0100] Melting point: 216°C

Elemental analysis for C <sub>26</sub> H <sub>26</sub> N <sub>4</sub> O <sub>2</sub> ·HCl·1.2H <sub>2</sub> O			
Calculated (%)	C:64.44	H: 6.12	N:11.56
Found (%)	C:64.59	H: 5.93	N:11.21

50

## Preparation Example 11

1-[1,5-Dimethyl-2-(4-fluorophenyl)indol-3-ylcarbonyl]-4-(2-pyridyl)piperazine dihydrochloride

55

[0101] Melting point: 159°C

EP 1 243 268 A1

Elemental analysis for C <sub>26</sub> H <sub>25</sub> FN <sub>4</sub> O·2HCl·0.75H <sub>2</sub> O			
Calculated (%)	C:60.64	H: 5.58	N:10.88
Found (%)	C:60.77	H: 5.49	N:10.53

5

Preparation Example 12

1-[1-Methyl-2-(4-hydroxyphenyl)indol-3-ylcarbonyl]-4-(2-pyridyl)piperazine hydrochloride

10

[0102] Melting point: 272°C

Elemental analysis for C <sub>25</sub> H <sub>24</sub> N <sub>4</sub> O <sub>2</sub> ·HCl			
Calculated (%)	C:66.88	H: 5.61	N:12.48
Found (%)	C:66.45	H: 5.60	N:12.35

15

Preparation Example 13

1-(1-Isopropyl-2-phenylindol-3-ylcarbonyl)-4-(2-pyridyl)piperazine hydrochloride

20

[0103] Melting point: 283°C

Elemental analysis for C <sub>27</sub> H <sub>28</sub> N <sub>4</sub> O·HCl			
Calculated (%)	C:70.35	H: 6.34	N:12.15
Found (%)	C:70.16	H: 6.48	N:12.13

25

Preparation Example 14

30 [0104] 1-(1-Methyl-2-phenylindol-3-ylcarbonyl)-4-(3-pyridyl)piperazine hydrochloride

[0104] Melting point: 277°C

35

Elemental analysis for C <sub>25</sub> H <sub>24</sub> N <sub>4</sub> O·HCl·0.9H <sub>2</sub> O			
Calculated (%)	C:66.85	H: 6.01	N:12.47
Found (%)	C:67.05	H: 5.92	N:12.44

40

Preparation Example 15

1-(1,5,6-Trimethyl-2-phenylindol-3-ylcarbonyl)-4-(2-pyridyl)piperazine hydrochloride

[0105] Melting point: 174°C

45

Elemental analysis for C <sub>27</sub> H <sub>28</sub> N <sub>4</sub> O·HCl·2.5H <sub>2</sub> O			
Calculated (%)	C:64.08	H: 6.77	N:11.07
Found (%)	C:64.20	H: 6.44	N:11.06

50

Preparation Example 16

1-(7-Methoxy-1-methyl-2-phenylindol-3-ylcarbonyl)-4-(2-pyridyl)-piperazine dihydrochloride

[0106] Melting point: 136°C

55

Elemental analysis for C <sub>26</sub> H <sub>26</sub> N <sub>4</sub> O <sub>2</sub> ·2HCl·0.8H <sub>2</sub> O			
Calculated (%)	C:60.77	H: 5.81	N:10.90

EP 1 243 268 A1

(continued)

Elemental analysis for C <sub>26</sub> H <sub>26</sub> N <sub>4</sub> O <sub>2</sub> ·2HCl·0.8H <sub>2</sub> O			
Found (%)	C:60.82	H: 6.11	N:10.82

5

Preparation Example 17

1-(6-Methoxy-1-methyl-2-phenylindol-3-ylcarbonyl)-4-(2-pyridyl)piperazine dihydrochloride

10

[0107] Melting point: 138°C

Elemental analysis for C <sub>26</sub> H <sub>26</sub> N <sub>4</sub> O <sub>2</sub> ·2HCl·1.25H <sub>2</sub> O			
Calculated (%)	C:59.83	H: 5.88	N:10.74
Found (%)	C:59.92	H: 5.83	N:10.78

15

Preparation Example 18

1-(1,6-Dimethyl-2-phenylindol-3-ylcarbonyl)-4-(2-pyridyl)piperazine hydrochloride

20

[0108] Melting point: 168-169°C

Elemental analysis for C <sub>26</sub> H <sub>26</sub> N <sub>4</sub> O·HCl·2.5H <sub>2</sub> O			
Calculated (%)	C:63.47	H: 6.55	N:11.39
Found (%)	C:63.38	H: 6.26	N:11.33

25

Preparation Example 19

30

1-[1-Methyl-2-(3-pyridyl)indol-3-ylcarbonyl]-4-(2-pyridyl)piperazine dihydrochloride

[0109] Melting point: 194°C

35

Elemental analysis for C <sub>24</sub> H <sub>23</sub> N <sub>5</sub> O·2HCl·5.1H <sub>2</sub> O			
Calculated (%)	C:51.27	H: 6.31	N:12.36
Found (%)	C:51.29	H: 6.01	N:11.90

40

Preparation Example 20  
1-(5-Fluoro-1-methyl-2-phenylindol-3-ylcarbonyl)-4-(2-pyridyl)piperazine hydrochloride

[0110] Melting point: 131°C

45

Elemental analysis for C <sub>25</sub> H <sub>23</sub> FN <sub>4</sub> O·HCl·1.5H <sub>2</sub> O			
Calculated (%)	C:58.37	H: 5.49	N:10.89
Found (%)	C:58.51	H: 5.35	N:10.87

50

Preparation Example 21

1-[1-Methyl-2-(4-methoxyphenyl)indol-3-ylcarbonyl]-4-(2-pyridyl)piperazine dihydrochloride.

55

[0111] Melting point: 133°C

Elemental analysis for C <sub>26</sub> H <sub>26</sub> N <sub>4</sub> O <sub>2</sub> ·2HCl·H <sub>2</sub> O			
Calculated (%)	C:60.35	H: 5.84	N:10.83

## EP 1 243 268 A1

(continued)

Elemental analysis for C <sub>26</sub> H <sub>26</sub> N <sub>4</sub> O <sub>2</sub> ·2HCl·H <sub>2</sub> O			
Found (96)	C:60.20	H: 6.03	N:10.93

5

Preparation Example 22

1-[1-Methyl-2-(2-thienyl)indol-3-ylcarbonyl]-4-(2-pyridyl)piperazine dihydrochloride

10

[0112] Melting point: 116°C

Elemental analysis for C <sub>23</sub> H <sub>22</sub> N <sub>4</sub> OS·2HCl·1.4H <sub>2</sub> O			
Calculated (%)	C:55.18	H: 5.39	N:11.19
Found (%)	C:55.48	H: 5.27	N:10.89

15

Preparation Example 23

2-[1-{4-(1-Methyl-2-phenylindol-3-ylcarbonyl)piperazinyl}]pyridine-1-oxide

20

[0113] Melting point: 113°C

Positive ion FAB-MS m/z: 413[M+H]<sup>+</sup>

25

Preparation Example 24

1-(1-Methyl-2-phenylindol-3-ylcarbonyl)-4-(6-hydroxy-2-pyridyl)-piperazine hydrochloride

[0114] Melting point: 177°C

30

Elemental analysis for C <sub>25</sub> H <sub>24</sub> N <sub>4</sub> O <sub>2</sub> ·HCl·1.9H <sub>2</sub> O			
Calculated (%)	C:62.15	H: 6.01	N:11.60
Found (%)	C:62.43	H: 6.30	N:11.19

35

Preparation Example 25

1-(1-Methyl-2-phenylindol-3-ylcarbonyl)-4-(4-pyridyl)piperazine hydrochloride

40

[0115] Melting point: 331°C

Elemental analysis for C <sub>25</sub> H <sub>24</sub> N <sub>4</sub> O·HCl·0.2H <sub>2</sub> O			
Calculated (%)	C:68.78	H: 5.86	N:12.83
Found (%)	C:68.77	H: 5.80	N:12.85

45

Preparation Example 26

1-(1-Methyl-2-phenylindol-3-ylcarbonyl)-4-(5-methyl-2-pyridyl) piperazine hydrochloride

50

[0116] Melting point: 202°C

Elemental analysis for C <sub>26</sub> H <sub>26</sub> N <sub>4</sub> O·HCl·1.8H <sub>2</sub> O			
Calculated (%)	C:65.14	H: 6.43	N:11.69
Found (%)	C:65.35	H: 6.42	N:11.39

55

EP 1 243 268 A1

Preparation Example 27

1-(4-Chloro-1-methyl-2-phenylindol-3-ylcarbonyl)-4-(2-pyridyl)piperazine hydrochloride

5 [0117] Melting point: 74°C

10

Elemental analysis for C <sub>25</sub> H <sub>23</sub> ClN <sub>4</sub> O·HCl·H <sub>2</sub> O			
Calculated (%)	C:61.86	H: 5.40	N:11.54
Found (%)	C:61.46	H: 5.79	N:11.48

Preparation Example 28

1-(6-Chloro-1-methyl-2-phenylindol-3-ylcarbonyl)-4-(2-pyridyl)piperazine hydrochloride

15

[0118] Melting point: 92°C

20

Elemental analysis for C <sub>25</sub> H <sub>23</sub> ClN <sub>4</sub> O·HCl·1.2H <sub>2</sub> O			
Calculated (%)	C:60.94	H: 5.36-	N:11.37
Found (%)	C:61.03	H: 5.47	N:11.60

Preparation Example 29

25

1-(1-Methyl-2-phenylindol-3-ylcarbonyl)-4-(5-methyl-2-pyridyl)piperazine dihydrochloride

[0119] Melting point: 249°C

30

Elemental analysis for C <sub>26</sub> H <sub>26</sub> N <sub>4</sub> O·2HCl·1.5H <sub>2</sub> O			
Calculated (%)	C:61.18	H: 6.12	N:10.98
Found (%)	C:61.12	H: 6.17	N:10.47

Preparation Example 30

35

1-(4-Fluoro-1-methyl-2-phenylindol-3-ylcarbonyl)-4-(2-pyridyl)piperazine hydrochloride

40

[0120] Melting point: 205°C

Elemental analysis for C <sub>25</sub> H <sub>23</sub> FN <sub>4</sub> O·HCl·2.5H <sub>2</sub> O			
Calculated (%)	C:60.54	H: 5.89	N:11.30
Found (%)	C:60.55	H: 5.73.	N:11.35

45

Preparation Example 31

50

1-(7-Fluoro-1-methyl-2-phenylindol-3-ylcarbonyl)-4-(2-pyridyl)piperazine hydrochloride

[0121] Melting point: 255°C

Elemental analysis for C <sub>25</sub> H <sub>23</sub> FN <sub>4</sub> O·HCl·2H <sub>2</sub> O			
Calculated (%)	C:61.66	H: 5.80	N:11.51
Found (%)	C:61.52	H: 5.60	N:11.38

55

EP 1 243 268 A1

Preparation Example 32

1-(1-Ethyl-2-phenylindol-3-ylcarbonyl)-4-(2-pyridyl)piperazine hydrochloride

5 [0122] Melting point: 233°C

10

Elemental analysis for C <sub>26</sub> H <sub>26</sub> N <sub>4</sub> O·HCl·0.5H <sub>2</sub> O			
Calculated (%)	C:68.49	H: 6.19	N:12.29
Found (%)	C:68.36	H: 6.19	N:12.29

Preparation Example 33

1-(1,5-Dimethyl-2-phenylindol-3-ylcarbonyl)-4-(3-pyridyl)piperazine dihydrochloride

15

[0123]

20

Elemental analysis for C <sub>26</sub> H <sub>26</sub> N <sub>4</sub> O·2HCl·3H <sub>2</sub> O			
Calculated (%)	C:58.10	H: 6.38	N:10.42
Found (%)	C:58.15	H: 6.07	N:10.33

Preparation Example 34

25 1-(1,5-Dimethyl-2-phenylindol-3-ylcarbonyl)-4-(4-pyridyl)piperazine hydrochloride

[0124] Melting point: 322°C

30

Elemental analysis for C <sub>26</sub> H <sub>26</sub> N <sub>4</sub> O·HCl·0.5H <sub>2</sub> O			
Calculated (%)	C:68.49	H: 6.19	N:12.29
Found (%)	C:68.75	H: 6.02	N:12.40

Preparation Example 35

35

1-[1-(2-Fluoroethyl)-2-phenylindol-3-ylcarbonyl]-4-(5-methyl-2-pyridyl)piperazine hydrochloride

[0125] Melting point: 151°C

40

Elemental analysis for C <sub>27</sub> H <sub>27</sub> FN <sub>4</sub> O·HCl·2H <sub>2</sub> O			
Calculated (%)	C:62.97	H: 6.26	N:10.88
Found (%)	C:63.09	H: 6.36	N:10.75

45 Preparation Example 36

45

1-[1-(2-Fluoroethyl)-2-phenylindol-3-ylcarbonyl]-4-(3-pyridyl)piperazine hydrochloride

[0126] Melting point: 217°C

50

Elemental analysis for C <sub>26</sub> H <sub>25</sub> FN <sub>4</sub> O·HCl·2.5H <sub>2</sub> O			
Calculated (%)	C:61.23	H: 6.13	N:10.99
Found (%)	C:61.29	H: 5.84	N:11.00

55

EP 1 243 268 A1

Preparation Example 37

1-(1-Ethyl-2-phenylindol-3-ylcarbonyl)-4-(5-methyl-2-pyridyl)piperazine hydrochloride

5 [0127] Melting point: 132°C

Elemental analysis for C <sub>27</sub> H <sub>28</sub> N <sub>4</sub> O·HCl·2.5H <sub>2</sub> O			
Calculated (%)	C:64.08	H: 6.77	N:11.07
Found (%)	C:64.11	H: 6.68	N:11.01

10

Preparation Example 38

1-(1,5,6-Trimethyl-2-phenylindol-3-ylcarbonyl)-4-(3-pyridyl)piperazine hydrochloride

15

[0128] Melting point: 260°C

Elemental analysis for C <sub>27</sub> H <sub>28</sub> N <sub>4</sub> O·HCl·0.7H <sub>2</sub> O			
Calculated (%)	C:68.47	H: 6.47	N:11.83
Found (%)	C:68.51	H: 6.40	N:11.88

20

Preparation Example 39

25 1-(1,5,6-Trimethyl-2-phenylindol-3-ylcarbonyl)-4-(4-pyridyl)piperazine hydrochloride

[0129] Melting point: 342°C

30

Elemental analysis for C <sub>27</sub> H <sub>28</sub> N <sub>4</sub> O·HCl·0.5H <sub>2</sub> O			
Calculated (%)	C:69.00	H: 6.43	N:11.92
Found (%)	C:68.72	H: 6.32	N:11.84

35

Preparation Example 40

35 1-(5-Chloro-1-methyl-2-phenylindol-3-ylcarbonyl)-4-(3-pyridyl)piperazine hydrochloride

40

[0130] Melting point: 120°C

Elemental analysis for C <sub>25</sub> H <sub>23</sub> ClN <sub>4</sub> O·HCl			
Calculated (%)	C:56.61	H: 5.89	N:10.56
Found (%)	C:56.44	H: 5.62	N:13.15

45

Preparation Example 41

1-(5-Chloro-1-methyl-2-phenylindol-3-ylcarbonyl)-4-(4-pyridyl)piperazine hydrochloride

50

[0131] Melting point: 216°C

Preparation Example 42

1-[1,5-Dimethyl-2-(3-trifluoromethylphenyl)indol-3-ylcarbonyl]-4-(2-pyridyl)piperazine hydrochloride

55

[0132] Melting point: 264°C

EP 1 243 268 A1

5

Elemental analysis for C <sub>27</sub> H <sub>25</sub> F <sub>3</sub> N <sub>4</sub> O·HCl·H <sub>2</sub> O			
Calculated (%)	C:60.84	H: 5.30	N:10.51
Found (%),	C:60.62	H: 5.48	N:10.51

Preparation Example 43

1-(1,5-Dimethyl-2-phenylindol-3-ylcarbonyl)-4-(3-pyridyl)piperazine-4-oxide

10 [0133] Melting point: 188°C

15

Elemental analysis for C <sub>26</sub> H <sub>26</sub> N <sub>4</sub> O <sub>2</sub> ·2.5H <sub>2</sub> O			
Calculated (%)	C:66.22	H: 6.63	N:11.88
Found (%)	C:66.23	H: 6.23	N:11.51

Preparation Example 44

1-(5-Fluoro-1-methyl-2-phenylindol-3-ylcarbonyl)-4-(3-pyridyl)piperazine hydrochloride

20 [0134] Melting point: 276°C

25

Elemental analysis for C <sub>25</sub> H <sub>23</sub> FN <sub>4</sub> O·HCl·H <sub>2</sub> O			
Calculated (%)	C:64.03	H: 5.59	N:11.95
Found (%)	C:64.37	H: 5.60	N:11.94

Preparation Example 45

1-(5-Fluoro-1-methyl-2-phenylindol-3-ylcarbonyl)-4-(4-pyridyl)piperazine hydrochloride

30 [0135] Melting point: 340°C

35

Elemental analysis for C <sub>25</sub> H <sub>23</sub> FN <sub>4</sub> O·HCl·H <sub>2</sub> O			
Calculated (%)	C:64.03	H: 5.59	N:11.95
Found (%)	C:63.99	H: 5.53	N:11.89

40 Preparation Example 46

1-(1,6-Dimethyl-2-phenylindol-3-ylcarbonyl)-4-(3-pyridyl)piperazine hydrochloride

45 [0136] Melting point: 199°C

50

Elemental analysis for C <sub>26</sub> H <sub>26</sub> N <sub>4</sub> O·HCl·1.2H <sub>2</sub> O			
Calculated (%)	C:66.64	H: 6.32	N:11.96
Found (%)	C:66.42	H: 6.44	N:11.73

55 Preparation Example 47

1-(1,6-Dimethyl-2-phenylindol-3-ylcarbonyl)-4-(4-pyridyl)piperazine hydrochloride

[0137] Melting point: 333°C

EP 1 243 268 A1

Elemental analysis for C <sub>26</sub> H <sub>26</sub> N <sub>4</sub> O·HCl			
Calculated (%)	C:69.87	H: 6.09	N:12.53
Found (%)	C:69.62	H: 6.18	N:12.47

5

Preparation Example 48

1-(1-Methyl-2-phenylindol-3-ylcarbonyl)-4-(5-nitro-2-pyridyl)piperazine hydrochloride

10

[0138] Melting point: 258°C

Elemental analysis for C <sub>25</sub> H <sub>23</sub> N <sub>5</sub> O <sub>3</sub> ·HCl			
Calculated (%)	C:62.83	H: 5.06	N:14.65
Found (%)	C:62.94	H: 5.26	N:14.59

15

Preparation Example 49

1-(1-Methyl-5,6-methylenedioxy-2-phenylindol-3-ylcarbonyl)-4-(2-pyridyl)piperazine hydrochloride

20

[0139] Melting point: 207°C

Elemental analysis for C <sub>26</sub> H <sub>24</sub> N <sub>4</sub> O <sub>3</sub> ·HCl·1.5H <sub>2</sub> O			
Calculated (%)	C:61.96	H: 5.60	N:11.12
Found (%)	C:62.16	H: 6.00	N:11.02

25

Preparation Example 50

30

1-[1-Methyl-2-(4-pyridyl)indol-3-ylcarbonyl]-4-(2-pyridyl)piperazine hydrochloride

[0140] Melting point: 233°C

35

Elemental analysis for C <sub>24</sub> H <sub>23</sub> N <sub>5</sub> O·HCl·H <sub>2</sub> O			
Calculated (%)	C:63.78	H: 5.80	N:15.50
Found (%)	C:64.08	H: 5.58	N:15.66

40

Preparation Example 51

1-[1-Methyl-2-(2,6-dimethoxyphenyl)indol-3-ylcarbonyl]-4-(2-pyridyl)piperazine hydrochloride

45

[0141] Melting point: 198°C

Elemental analysis for C <sub>27</sub> H <sub>28</sub> N <sub>4</sub> O <sub>3</sub> ·HCl·2H <sub>2</sub> O			
Calculated (%)	C:61.30	H: 6.29	N:10.59
Found (%)	C:61.45	H: 6.60	N:10.57

50

Preparation Example 52

1-(1,4-Dimethyl-2-phenylindol-3-ylcarbonyl)-4-(2-pyridyl)piperazine hydrochloride

55

[0142] Melting point: 210°C

Elemental analysis for C <sub>26</sub> H <sub>26</sub> N <sub>4</sub> O·HCl·H <sub>2</sub> O			
Calculated (%)	C:67.16	H: 6.29	N:12.05

(continued)

Elemental analysis for C <sub>26</sub> H <sub>26</sub> N <sub>4</sub> O·HCl·H <sub>2</sub> O			
Calculated (%)	C:67.45	H: 6.11	N:12.24
Found (%)			

5

Preparation Example 53

1-[1,5-Dimethyl-2-(3-methoxyphenyl)indol-3-ylcarbonyl]-4-(2-pyridyl)piperazine hydrochloride

10

[0143] Melting point: 137°C

Elemental analysis for C <sub>27</sub> H <sub>28</sub> N <sub>4</sub> O <sub>2</sub> ·HCl·1.5H <sub>2</sub> O			
Calculated (%)	C:64.34	H: 6.40	N:11.12
Found (%)	C:64.10	H: 6.79	N:11.02

15

Preparation Example 54

1-(1-Methyl-2-phenylindol-3-ylcarbonyl)-4-(3-pyridyl)piperazine-4-oxide

20

[0144] Melting point: 192°C

Elemental analysis for C <sub>25</sub> H <sub>24</sub> N <sub>4</sub> O <sub>2</sub> ·2H <sub>2</sub> O			
Calculated (%)	C:66.95	H: 6.29	N:12.49
Found (%)	C:67.13	H: 6.20	N:12.26

25

Preparation Example 55

30

1-[1-Methyl-2-(2-thienyl)indol-3-ylcarbonyl]-4-(3-pyridyl)piperazine hydrochloride

35

[0145] Melting point: 237°C

Elemental analysis for C <sub>23</sub> H <sub>22</sub> N <sub>4</sub> O <sub>2</sub> ·HCl·0.5H <sub>2</sub> O			
Calculated (%)	C:61.67	H: 5.40	N:12.51
Found (%)	C:61.41	H: 5.34	N:13.12

40

Preparation Example 56  
1-[1,5-Dimethyl-2-(4-methylphenyl)indol-3-ylcarbonyl]-4-(2-pyridyl)piperazine hydrochloride

45

[0146] Melting point: 237°C

45

Preparation Example 57

50

1-[1,5-Dimethyl-2-(4-nitrophenyl)indol-3-ylcarbonyl]-4-(2-pyridyl)piperazine hydrochloride

55

[0147] Melting point: 198°C

Elemental analysis for C <sub>26</sub> H <sub>25</sub> N <sub>5</sub> O <sub>3</sub> ·HCl·1.5H <sub>2</sub> O			
Calculated (%)	C:60.17	H: 5.63	N:13.49
Found (%)	C:59.90	H: 5.66	N:13.28

55

## Preparation Example 58

1-(1,5-Dimethyl-2-phenylindol-3-ylcarbonyl)-4-(5-nitro-2-pyridyl)piperazine hydrochloride

5 [0148] Melting point: 233°C

10

Elemental analysis for C <sub>26</sub> H <sub>25</sub> N <sub>5</sub> O <sub>3</sub> ·HCl·2.3H <sub>2</sub> O			
Calculated (%)	C:58.54	H: 5.78	N:13.13
Found (%)	C:58.30	H: 5.33	N:13.04

## Preparation Example 59

1-(1,5-Dimethyl-2-phenylindol-3-ylcarbonyl)-4-(5-methanesulfonamino-2-pyridyl)piperazine dihydrochloride

15

[0149] Melting point: 192°C

20

Elemental analysis for C <sub>27</sub> H <sub>29</sub> N <sub>5</sub> O <sub>3</sub> S·2HCl·2H <sub>2</sub> O			
Calculated (%)	C:52.94	H: 5.76	N:11.43
Found (%)	C:52.79	H: 5.36	N:11.56

## Preparation Example 60

25

N-(endo-8-Methyl-8-azabicyclo[3.2.1]octa-3-yl)-1-methyl-2-phenylindole-3-carboxamide hydrochloride

[0150] Melting point: 132-142°C

30

Elemental analysis for C <sub>24</sub> H <sub>27</sub> N <sub>3</sub> O·HCl·3.5H <sub>2</sub> O			
Calculated (%)	C:60.94	H: 7.46	N:8.88
Found (%)	C:60.84	H: 7.23	N:8.57

## Preparation Example 61

35

N-(endo-8-Methyl-8-azabicyclo[3.2.1]octa-3-yl)-5-methoxy-1-methyl-2-phenylindole-3-carboxamide hydrochloride

[0151] Melting point: 210°C

40

Elemental analysis for C <sub>25</sub> H <sub>29</sub> N <sub>3</sub> O <sub>2</sub> ·HCl·H <sub>2</sub> O			
Calculated (%)	C:65.56	H: 7.04	N:9.17
Found (%)	C:65.59	H: 6.95	N:9.18

## Preparation Example 62

45

N-(endo-8-Methyl-8-azabicyclo[3.2.1]octa-3-yl)-1,7-dimethyl-2-phenylindole-3-carboxamide hydrochloride

[0152] Melting point: 261°C

50

Elemental analysis for C <sub>25</sub> H <sub>29</sub> N <sub>3</sub> O·HCl·2H <sub>2</sub> O			
Calculated (%)	C:63.08	H: 7.19	N:8.82
Found (%)	C:62.68	H: 7.03	N:8.93

55

EP 1 243 268 A1

Preparation Example 63

N-(endo-8-Methyl-8-azabicyclo[3.2.1]octa-3-yl)-1,6-dimethyl-2-phenylindole-3-carboxamide hydrochloride

5 [0153] Melting point: 142°C

Elemental analysis for C <sub>25</sub> H <sub>29</sub> N <sub>3</sub> O·HCl·0.7H <sub>2</sub> O			
Calculated (%)	C:68.78	H: 7.25	N:9.62
Found (%)	C:68.60	H: 7.26	N:9.73

10

Preparation Example 64

N-(endo-8-Methyl-8-azabicyclo[3.2.1]octa-3-yl)-5-chloro-1-methyl-2-phenylindole-3-carboxamide hydrochloride

15

[0154] Melting point: 247°C

Elemental analysis for C <sub>24</sub> H <sub>26</sub> ClN <sub>3</sub> O·HCl·2H <sub>2</sub> O			
Calculated (%)	C:60.00	H: 6.50	N:8.75
Found (%)	C:59.99	H: 6.34	N:8.74

20

Preparation Example 65

25 N-(endo-8-Methyl-8-azabicyclo[3.2.1]octa-3-yl)-1-methyl-2-(4-pyridyl)indole-3-carboxamide

[0155] Melting point: 157°C

30

Elemental analysis for C <sub>23</sub> H <sub>26</sub> N <sub>4</sub> O			
Calculated (%)	C:73.77	H: 7.00	N:14.96
Found (%)	C:73.46	H: 7.11	N:14.84

Preparation Example 66

35

N-(endo-8-Methyl-8-azabicyclo[3.2.1]octa-3-yl)-1-methyl-2-(3-pyridyl)indole-3-carboxamide

[0156] Melting point: 145°C

40

Elemental analysis for C <sub>23</sub> H <sub>26</sub> N <sub>4</sub> O·0.2H <sub>2</sub> O			
Calculated (%)	C:73.07	H: 7.04	N:14.82
Found (%)	C:73.11	H: 6.97	N:14.81

45

Preparation Example 67

N-(endo-8-Methyl-8-azabicyclo[3.2.1]octa-3-yl)-5-fluoro-1-methyl-2-phenylindole-3-carboxamide hydrochloride

50

[0157] Melting point: 315°C

Elemental analysis for C <sub>24</sub> H <sub>26</sub> FN <sub>3</sub> O·HCl·0.5H <sub>2</sub> O			
Calculated (%)	C:65.97	H: 6.46	N:9.62
Found (%)	C:66.03	H: 6.43	N:9.56

55

EP 1 243 268 A1

Preparation Example 68

N-(endo-8-Methyl-8-azabicyclo[3.2.1]octa-3-yl)-1-methyl-2-(2-naphthyl)indole-3-carboxamide

5 [0158] Melting point: 185°C

Elemental analysis for C <sub>28</sub> H <sub>29</sub> N <sub>3</sub> O·0.25H <sub>2</sub> O			
Calculated (%)	C:78.57	H: 6.95	N:9.82
Found (%)	C:78.50	H: 7.00	N:9.87

10

Preparation Example 69

N-(endo-8-Methyl-8-azabicyclo[3.2.1]octa-3-yl)-7-chloro-1-methyl-2-phenylindole-3-carboxamide hydrochloride

15

[0159] Melting point: 156-157°C

Elemental analysis for C <sub>24</sub> H <sub>26</sub> ClN <sub>3</sub> O·HCl·1.5H <sub>2</sub> O			
Calculated (%)	C:61.15	H: 6.41	N:8.91
Found (%)	C:61.02	H: 6.14	N:8.93

20

Preparation Example 70

25 N-(endo-8-Methyl-8-azabicyclo[3.2.1]octa-3-yl)-5-bromo-1-methyl-2-phenylindole-3-carboxamide hydrochloride

[0160] Melting point: 192°C

Elemental analysis for C <sub>24</sub> H <sub>26</sub> BrN <sub>3</sub> O·HCl·2.5H <sub>2</sub> O			
Calculated (%)	C:53.99	H: 6.04	N:7.87
Found (%)	C:54.23	H: 5.69	N:8.05

30

Preparation Example 71

35

N-(endo-8-Methyl-8-azabicyclo[3.2.1]octa-3-yl)-5-cyano-1-methyl-2-phenylindole-3-carboxamide hydrochloride

[0161] Melting point: 328-329°C

Elemental analysis for C <sub>25</sub> H <sub>26</sub> N <sub>4</sub> O·HCl·1.25H <sub>2</sub> O			
Calculated (%)	C:65.64	H: 6.50	N:12.25
Found (%)	C:65.37	H: 6.10	N:12.13

40

Preparation Example 72

45

N-(endo-8-Methyl-8-azabicyclo[3.2.1]octa-3-yl)-6-chloro-1-methyl-2 phenylindole-3-carboxamide hydrochloride

50

[0162] Melting point: 184°C

Elemental analysis for C <sub>24</sub> H <sub>26</sub> ClN <sub>3</sub> O·HCl·2H <sub>2</sub> O			
Calculated (%)	C:60.00	H: 6.50	N:8.75
Found (%)	C:60.27	H: 6.13	N:9.12

55

## Preparation Example 73

N-(endo-8-Methyl-8-azabicyclo[3.2.1]octa-3-yl)-4-chloro-1-methyl-2-phenylindole-3-carboxamide hydrochloride

- 5 [0163] Melting point: 308-309°C  
EI-MS m/z: 407[M]<sup>+</sup>

## Preparation Example 74

N-(endo-8-Methyl-8-azabicyclo[3.2.1]octa-3-yl)-1-methyl-2-(2-thienyl)indole-3-carboxamide hydrochloride

- 10 [0164] Melting point: 330°C

Elemental analysis for C <sub>22</sub> H <sub>25</sub> N <sub>3</sub> OS·HCl·0.25H <sub>2</sub> O			
Calculated (%)	C:62.84 C:62.84	H: 6.35 H: 6.31	N:9.90 N:9.85
Found (%)			

## Preparation Example 75

N-(endo-8-Methyl-8-azabicyclo[3.2.1]octa-3-yl)-7-fluoro-1-methyl-2-phenylindole-3-carboxamide hydrochloride

- 20 [0165] Melting point: 202°C

Elemental analysis for C <sub>24</sub> H <sub>26</sub> FN <sub>3</sub> O·HCl·1.6H <sub>2</sub> O			
Calculated (%)	C:63.11 C:62.93	H: 6.66 H: 6.31	N:9.20 N:9.05
Found (%)			

## Preparation Example 76

N-(endo-8-Methyl-8-azabicyclo[3.2.1]octa-3-yl)-7-methoxy-1-methyl-2-phenylindole-3-carboxamide hydrochloride

- 30 [0166] Melting point: 234°C  
EI-MS m/z: 403[M]<sup>+</sup>

## Preparation Example 77

N-(endo-8-Methyl-8-azabicyclo[3.2.1]octa-3-yl)-6-fluoro-1-methyl-2-phenylindole-3-carboxamide hydrochloride

- 40 [0167] Melting point: 224°C  
EI-MS m/z: 391[M]<sup>+</sup>

## Preparation Example 78

N-(endo-8-Methyl-8-azabicyclo[3.2.1]octa-3-yl)-4-fluoro-1-methyl-2-phenylindole-3-carboxamide hydrochloride

- 45 [0168] Melting point: 259°C  
EI-MS m/z: 391[M]<sup>+</sup>

## Preparation Example 79

N-(endo-8-Methyl-8-azabicyclo[3.2.1]octa-3-yl)-6-methoxy-1-methyl-2-phenylindole-3-carboxamide hydrochloride

- 50 [0169] Melting point: 176°C  
EI-MS m/z: 403[M]<sup>+</sup>

## Preparation Example 80

N-(endo-8-Methyl-8-azabicyclo[3.2.1]octa-3-yl)-1-isopropyl-2-phenylindole-3-carboxamide hydrochloride

5 [0170] Melting point: 301°C

Elemental analysis for C <sub>26</sub> H <sub>31</sub> N <sub>3</sub> O·HCl·H <sub>2</sub> O			
Calculated (%)	C:68.48	H: 7.51	N:9.21
Found (%)	C:68.86	H: 7.33	N:9.23

10

## Preparation Example 81

N-(endo-8-Benzyl-8-azabicyclo[3.2.1]octa-3-yl)-1,5-dimethyl-2-phenylindole-3-carboxamide hydrochloride

15

[0171] Melting point: 228°C  
EI-MS m/z: 463[M]<sup>+</sup>

20

N-(endo-8-Methyl-8-azabicyclo[3.2.1]octa-3-yl)-7-bromo-1-methyl-2-phenylindole-3-carboxamide hydrochloride

[0172] Melting point: 182-183°C

25

Elemental analysis for C <sub>24</sub> H <sub>26</sub> BrN <sub>3</sub> O·HCl·1.5H <sub>2</sub> O			
Calculated (%)	C:55.88	H: 5.86	N:8.15
Found (%)	C:55.43	H: 5.43	N:8.12

30

## Preparation Example 83

N-(endo-8-Methyl-8-azabicyclo[3.2.1]octa-3-yl)-6-bromo-1-methyl-2-phenylindole-3-carboxamide hydrochloride

35

[0173] Melting point: 183°C

Elemental analysis for C <sub>24</sub> H <sub>26</sub> BrN <sub>3</sub> O·HCl·1.75H <sub>2</sub> O			
Calculated (%)	C:55.39	H: 5.91	N:8.07
Found (%)	C:55.12	H: 5.32	N:7.99

40

## Preparation Example 84

N-(endo-8-Acetyl-8-azabicyclo[3.2.1]octa-3-yl)-1,5-dimethyl-2-phenylindole-3-carboxamide

45

[0174] Melting point: 226-231°C

Elemental analysis for C <sub>26</sub> H <sub>29</sub> N <sub>3</sub> O <sub>2</sub> ·0.4H <sub>2</sub> O			
Calculated (%)	C:73.87	H: 7.11	N:9.94
Found (%)	C:73.82	H: 6.97	N:9.86

50

## Preparation Example 85

N-(endo-8-Methanesulfonyl-8-azabicyclo[3.2.1]octa-3-yl)-1,5-dimethyl-2-phenylindole-3-carboxamide

55

[0175] Melting point: 210-214°C

5

Elemental analysis for C <sub>25</sub> H <sub>29</sub> N <sub>3</sub> O <sub>3</sub> S			
Calculated (%)	C:66.49	H: 6.47	N:9.30
Found (%)	C:66.21	H: 6.49	N:9.13

## Preparation Example 86

N-(endo-8-Methyl-8-azabicyclo[3.2.1]octa-3-yl)-1-methyl-2-(4-methoxyphenyl)indole-3-carboxamide hydrochloride

10

[0176] Melting point: 252°C

15

Elemental analysis for C <sub>25</sub> H <sub>29</sub> N <sub>3</sub> O <sub>2</sub> ·HCl·H <sub>2</sub> O			
Calculated (%)	C:65.56	H: 7.04	N:9.17
Found (%)	C:65.67	H: 7.09	N:9.24

## Preparation Example 87

N-(endo-8-Methyl-8-azabicyclo[3.2.1]octa-3-yl)-1-methyl-2-(4-chlorophenyl)indole-3-carboxamide hydrochloride

20

[0177] Melting point: 263°C

25

Elemental analysis for C <sub>24</sub> H <sub>26</sub> ClN <sub>3</sub> O·HCl·H <sub>2</sub> O			
Calculated (%)	C:62.34	H: 6.32	N:9.09
Found (%)	C:62.14	H: 6.66	N:9.10

## Preparation Example 88

30

N-(endo-8-Methyl-8-azabicyclo[3.2.1]octa-3-yl)-4-bromo-1-methyl-2-phenylindole-3-carboxamide hydrochloride

[0178] Melting point: 322°C

EI-MS m/z: 451[M]<sup>+</sup>

35

## Preparation Example 89

N-(endo-8-Methyl-8-azabicyclo[3.2.1]octa-3-yl)-1-methyl-2-(4-methylphenyl)indole-3-carboxamide hydrochloride

40

[0179] Melting point: 268-269°C

Positive ion FAB-MS m/z: 388[M+H]<sup>+</sup>

## Preparation Example 90

45

N-(endo-8-Methyl-8-azabicyclo[3.2.1]octa-3-yl)-1-methyl-2-(4-fluorophenyl)indole-3-carboxamide hydrochloride

[0180] Melting point: 302°C

Positive ion FAB-MS m/z: 392[M+H]<sup>+</sup>

50

## Preparation Example 91

N-(endo-8-Methyl-8-azabicyclo[3.2.1]octa-3-yl)-1-methyl-2-(4-hydroxyphenyl)indole-3-carboxamide hydrochloride

[0181] Melting point: 338°C

Positive ion FAB-MS m/z: 390[M+H]<sup>+</sup>

55

EP 1 243 268 A1

Preparation Example 92

N-(endo-8-Azabicyclo[3.2.1]octa-3-yl)-1,5-dimethyl-2-phenylindole-3-carboxamide hydrochloride

5 [0182] Melting point: 323°C

10

Elemental analysis for C <sub>24</sub> H <sub>27</sub> N <sub>3</sub> O·HCl·2H <sub>2</sub> O			
Calculated (%)	C:64.63	H: 7.23	N:9.42
Found (%)	C:64.80	H: 7.06	N:9.44

Preparation Example 93

N-(endo-8-Benzyl-8-azabicyclo[3.2.1]octa-3-yl)-1-methyl-2-phenylindole-3-carboxamide hydrochloride

15

[0183] Melting point: 273°C  
EI-MS m/z: 449[M]+

20

Preparation Example 94

N-(endo-8-Formyl-8-azabicyclo[3.2.1]octa-3-yl)-1-methyl-2-phenylindole-3-carboxamide

25

[0184] Melting point: 256°C

30

Elemental analysis for C <sub>24</sub> H <sub>25</sub> N <sub>3</sub> O <sub>2</sub>			
Calculated (%)	C:74.39	H: 6.50	N:10.84
Found (%).	C:74.20	H: 6.53	N:10.99

35

Preparation Example 95

N-(endo-8-Methyl-8-azabicyclo[3.2.1]octa-3-yl)-1,5,6-trimethyl-2-phenylindole-3-carboxamide hydrochloride

40

[0185] Melting point: 280°C

45

Elemental analysis for C <sub>26</sub> H <sub>31</sub> N <sub>3</sub> O·HCl·1.25H <sub>2</sub> O			
Calculated (%)	C:67.81	H: 7.55	N:9.12
Found (%)	C:67.81	H: 7.22	N:9.27

50

Preparation Example 96

N-(endo-8-Methyl-8-azabicyclo[3.2.1]octa-3-yl)-1,4,5-trimethyl-2-phenylindole-3-carboxamide hydrochloride

55

[0186] Melting point: 264°C  
EI-MS m/z: 401[M]+

60

Preparation Example 97

65

N-(endo-8-Methyl-8-azabicyclo[3.2.1]octa-3-yl)-1-methyl-2-(3-trifluoromethylphenyl)indole-3-carboxamide hydrochloride

70

[0187] Melting point: 230°C

75

Elemental analysis for C <sub>25</sub> H <sub>26</sub> F <sub>3</sub> N <sub>3</sub> O·HCl·1.5H <sub>2</sub> O			
Calculated (%)	C:59.46	H: 5.99	N:8.32
Found (%)	C:59.36	H: 5.78	N:8.34

EP 1 243 268 A1

Preparation Example 98

N-(endo-8-Methyl-8-azabicyclo[3.2.1]octa-3-yl)-1-methyl-2-(3-trifluoromethoxyphenyl)indole-3-carboxamide hydrochloride

5

[0188] Melting point: 261°C

10

Elemental analysis for C <sub>25</sub> H <sub>26</sub> F <sub>3</sub> N <sub>3</sub> O <sub>2</sub> ·HCl·1.5H <sub>2</sub> O			
Calculated (%)	C:57.64 C:58.04	H: 5.80 H: 5.56	N:8.07 N:8.36
Found (%)			

Preparation Example 99

15 N-(endo-8-Methyl-8-azabicyclo[3.2.1]octa-3-yl)-1-methyl-2-(3-methoxyphenyl)indole-3-carboxamide hydrochloride

20

[0189] Melting point: 262°C.

Elemental analysis for C <sub>25</sub> H <sub>29</sub> N <sub>3</sub> O <sub>2</sub> ·HCl·H <sub>2</sub> O			
Calculated (%)	C:65.56 C:65.85	H: 7.04 H: 6.79	N:9.17 N:9.24
Found (%)			

Preparation Example 100

25 N-(endo-8-Methyl-8-azabicyclo[3.2.1]octa-3-yl)-1-methyl-2-(4-nitrophenyl)indole-3-carboxamide hydrochloride

[0190] Melting point: 244°C

30

Elemental analysis for C <sub>24</sub> H <sub>26</sub> N <sub>4</sub> O <sub>3</sub> ·HCl·2H <sub>2</sub> O			
Calculated (%)	C:58.71 C:58.68	H: 6.36 H: 5.94	N:11.41 N:11.33
Found (%)			

35

Preparation Example 101

N-(endo-8-Methyl-8-azabicyclo[3.2.1]octa-3-yl)-1-benzyl-2-phenylindole-3-carboxamide hydrochloride

[0191] Melting point: 131°C

40 EI-MS m/z: 449[M]<sup>+</sup>

Preparation Example 102

N-(endo-8-Methyl-8-azabicyclo[3.2.1]octa-3-yl)-1-ethyl-2-phenylindole-3-carboxamide hydrochloride

45 [0192] Melting point: 192°C

EI-MS m/z: 387[M]<sup>+</sup>

Preparation Example 103

50 N-[endo-8-(4-Methyl-3-pentenyl)-8-azabicyclo[3.2.1]octa-3-yl]-1,5-dimethyl-2-phenylindole-3-carboxamide hydrochloride

55 [0193] Melting point: 254°C

EI-MS m/z: 455[M]<sup>+</sup>

EP 1 243 268 A1

Preparation Example 104

N-(endo-8-Isopropyl-8-azabicyclo[3.2.1]octa-3-yl)-1-methyl-2-phenylindole-3-carboxamide hydrochloride

- 5 [0194] Melting point: 303°C  
EI-MS m/z: 401[M]<sup>+</sup>

Preparation Example 105

10 N-(endo-8-Cyclopropylmethyl-8-azabicyclo[3.2.1]octa-3-yl)-1-methyl-2-phenylindole-3-carboxamide hydrochloride

- [0195] Melting point: 245°C  
EI-MS m/z: 401[M]<sup>+</sup>

15	Elemental analysis for C <sub>27</sub> H <sub>31</sub> N <sub>3</sub> O·HCl·2H <sub>2</sub> O			
Calculated (%)	C:66.72	H: 7.47	N:8.64	
Found (%)	C:66.84	H: 7.02	N:8.58	

20 Preparation Example 106

N-[endo-8-(2,2,2-Trifluoroethyl)-8-azabicyclo[3.2.1]octa-3-yl]-1-methyl-2-phenylindole-3-carboxamide hydrochloride

- [0196] Melting point: 247°C

25	Elemental analysis for C <sub>25</sub> H <sub>26</sub> F <sub>3</sub> N <sub>3</sub> O·HCl·1.5H <sub>2</sub> O			
Calculated (%)	C:59.46	H: 5.99	N:8.32	
Found (%)	C:59.45	H: 5.94	N:8.12	

30 Preparation Example 107

N-(endo-8-Methyl-8-azabicyclo[3.2.1]octa-3-yl)-1-methyl-2-(2-fluorophenyl)indole-3-carboxamide hydrochloride

- 35 [0197] Melting point: 206°C

40	Elemental analysis for C <sub>24</sub> H <sub>26</sub> FN <sub>3</sub> O·HCl·1.5H <sub>2</sub> O			
Calculated (%)	C:63.36	H: 6.65	N:9.24	
Found (%)	C:63.74	H: 6.57	N:9.43	

Preparation Example 108

N-(endo-8-Methyl-8-azabicyclo[3.2.1]octa-3-yl)-1-methyl-2-(2-bromophenyl)indole-3-carboxamide hydrochloride

- 45 [0198] Melting point: 252°C

50	Elemental analysis for C <sub>24</sub> H <sub>26</sub> BrN <sub>3</sub> O·HCl·0.75H <sub>2</sub> O			
Calculated (%)	C:57.38	H: 5.72	N:8.60	
Found (%)	C:57.43	H: 5.56	N:8.44	

Preparation Example 109

N-(endo-8-Methyl-8-azabicyclo[3.2.1]octa-3-yl)-1-methyl-2-(2-nitrophenyl)indole-3-carboxamide hydrochloride

- 55 [0199] Melting point: 191°C

5

Elemental analysis for C <sub>24</sub> H <sub>26</sub> N <sub>4</sub> O <sub>3</sub> ·HCl·1.5H <sub>2</sub> O			
Calculated (%)	C:59.81 C:59.40	H: 6.27 H: 5.94	N:11.62 N:12.24
Found (%)			

## Preparation Example 110

N-(endo-8-Methyl-8-azabicyclo[3.2.1]octa-3-yl)-1,5-dimethyl-2-(4-fluorophenyl)indole-3-carboxamide hydrochloride

10

[0200] Melting point: 295°C

15

Elemental analysis for C <sub>25</sub> H <sub>28</sub> FN <sub>3</sub> O·HCl·H <sub>2</sub> O			
Calculated (%)	C:65.28 C:65.15	H: 6.79 H: 6.42	N:9.14 N:9.22
Found (%)			

## Preparation Example 111

20

N-(endo-8-Azabicyclo[3.2.1]octa-3-yl)-5-chloro-1-methyl-2-phenylindole-3-carboxamide hydrochloride

[0201] Melting point: 365°C

EI-MS m/z: 393[M]<sup>+</sup>

25

## Preparation Example 112

N-(endo-8-Azabicyclo[3.2.1]octa-3-yl)-1-methyl-2-(4-fluorophenyl)indole-3-carboxamide hydrochloride

[0202] Melting point: 329°C

30

EI-MS m/z: 377[M]<sup>+</sup>

35

## Preparation Example 113

N-(endo-8-Azabicyclo[3.2.1]octa-3-yl)-5-methoxy-1-methyl-2-phenylindole-3-carboxamide hydrochloride

[0203] Melting point: 350°C

EI-MS m/z: 389[M]<sup>+</sup>

40

## Preparation Example 114

N-(endo-8-Azabicyclo[3.2.1]octa-3-yl)-1,6-dimethyl-2-phenylindole-3-carboxamide hydrochloride

[0204] Melting point: 324°C

EI-MS m/z: 373[M]<sup>+</sup>

45

## Preparation Example 115

N-(endo-8-Methyl-8-azabicyclo[3.2.1]octa-3-yl)-1,6-dimethyl-2-(4-fluorophenyl)indole-3-carboxamide hydrochloride

50

[0205] Melting point: 304°C

55

Elemental analysis for C <sub>25</sub> H <sub>28</sub> FN <sub>3</sub> O·HCl·0.75H <sub>2</sub> O			
Calculated (%)	C:65.92 C:65.74	H: 6.75 H: 7.06	N:9.23 N:8.74
Found (%)			

## Preparation Example 116

N-(endo-8-Methyl-8-azabicyclo[3.2.1]octa-3-yl)-1,5-dimethyl-2-(4-hydroxyphenyl)indole-3-carboxamide hydrochloride

5

[0206] Melting point: 343°C

10

Elemental analysis for C <sub>25</sub> H <sub>29</sub> N <sub>3</sub> O <sub>2</sub> ·HCl·3.25H <sub>2</sub> O			
Calculated (%)	C:60.23	H: 7.38	N:8.43
Found (%)	C:60.25	H: 6.84	N:8.68

## Preparation Example 117

15 N-(endo-8-Methyl-8-azabicyclo[3.2.1]octa-3-yl)-1,5-dimethyl-2-phenylindole-3-carboxamide hydrochloride

[0207] Melting point: 252°C

20

Elemental analysis for C <sub>25</sub> H <sub>29</sub> N <sub>3</sub> O·HCl·1.5H <sub>2</sub> O			
Calculated (%)	C:66.58	H: 7.38	N:9.32
Found (%)	C:66.12	H: 6.89	N:9.81

25

EI-MS m/z: 387[M]<sup>+</sup>

Preparation Example 118

1-(1-Methyl-2-phenylindol-3-ylcarbonyl)-4-(2-pyridyl) homopiperazine dihydrochloride

[0208]

35

Elemental analysis for C <sub>26</sub> H <sub>26</sub> N <sub>4</sub> O·2HCl·3H <sub>2</sub> O			
Calculated (%)	C:58.10	H: 6.38	N:10.42
Found (%)	C:58.46	H: 6.34	N:10.16

## Preparation Example 119

1-(1,5-Dimethyl-2-phenylindol-3-ylcarbonyl)-4-(2-pyridyl)homopiperazine hydrochloride

40

[0209] Melting point: 191-194°C

45

Elemental analysis for C <sub>27</sub> H <sub>28</sub> N <sub>4</sub> O·HCl·0.5H <sub>2</sub> O			
Calculated (%)	C:69.00	H: 6.43	N:11.92
Found (%)	C:69.17	H: 6.37	N:11.97

## Preparation Example 120

1-(1-Methyl-2-phenylindol-3-ylcarbonyl)-4-(3-pyridyl)homopiperazine hydrochloride

50

[0210] Melting point: 268-271°C

55

Elemental analysis for C <sub>26</sub> H <sub>26</sub> N <sub>4</sub> O·HCl			
Calculated (%)	C:69.87	H: 6.09	N:12.53
Found (%)	C:69.60	H: 6.20	N:12.68

**EP 1 243 268 A1**

Preparation Example 121

1-(1,5-Dimethyl-2-phenylindol-3-ylcarbonyl)-4-(3-pyridyl)homopiperazine hydrochloride

5 [0211] Melting point: 214-217°C

Elemental analysis for C <sub>27</sub> H <sub>28</sub> N <sub>4</sub> O·HCl			
Calculated (%)	C:70.35	H: 6.34	N:12.15
Found (%)	C:70.30	H: 6.43	N:12.26

10

Preparation Example 122

1-(1,5-Dimethyl-2-phenylindol-3-ylcarbonyl)-4-(5-cyano-2-pyridyl)homopiperazine

15 [0212] Melting point: 230-231°C

Elemental analysis for C <sub>28</sub> H <sub>27</sub> N <sub>5</sub> O·0.25H <sub>2</sub> O			
Calculated (%)	C:74.07	H: 6.10	N:15.42
Found (%)	C:73.85	H: 6.04	N:15.59

20

Preparation Example 123

25 1-(1,5-Dimethyl-2-phenylindol-3-ylcarbonyl)-4-(5-trifluoromethyl-2-pyridyl)homopiperazine hydrochloride

[0213] Melting point: 189-192°C

Elemental analysis for C <sub>28</sub> H <sub>27</sub> F <sub>3</sub> N <sub>4</sub> O·HCl			
Calculated (%)	C:63.57	H: 5.33	N:10.59
Found (%)	C:63.39	H: 5.31	N:10.53

30

Preparation Example 124

35 1-[1,5-Dimethyl-2-(4-methylphenyl)indol-3-ylcarbonyl]-4-(2-pyridyl)homopiperazine hydrochloride

[0214] Melting point: 167-170°C

Elemental analysis for C <sub>28</sub> H <sub>30</sub> N <sub>4</sub> O·HCl·0.75H <sub>2</sub> O			
Calculated (%)	C:68.84	H: 6.71	N:11.47
Found (%)	C:68.64	H: 6.76	N:11.28

40

Preparation Example 125

45 1-[1,5-Dimethyl-2-(4-nitrophenyl)indol-3-ylcarbonyl]-4-(2-pyridyl)homopiperazine hydrochloride

[0215] Melting point: 247-249°C

Elemental analysis for C <sub>27</sub> H <sub>27</sub> N <sub>5</sub> O <sub>3</sub> ·HCl·0.25H <sub>2</sub> O			
Calculated (%)	C:63.52	H: 5.63	N:13.72
Found (%)	C:63.89	H: 5.63	N:13.48

45

50

EP 1 243 268 A1

Preparation Example 126

1-[1,5-Dimethyl-2-(3-trifluoromethoxyphenyl)indol-3-ylcarbonyl]-4-(2-pyridyl)homopiperazine hydrochloride

5 [0216] Melting point: 155-158°C

Elemental analysis for C <sub>28</sub> H <sub>27</sub> F <sub>3</sub> N <sub>4</sub> O <sub>2</sub> ·HCl·0.25H <sub>2</sub> O			
Calculated (%)	C:61.20	H: 5.23	N:10.20
Found (%)	C:61.27	H: 5.16	N:10.21

10

Preparation Example 127

1-[(1,5-Dimethyl-2-(2-methoxyphenyl)indol-3-ylcarbonyl)]-4-(2-pyridyl)homopiperazine hydrochloride

15

[0217] Melting point: 181-184°C

Elemental analysis for C <sub>28</sub> H <sub>30</sub> N <sub>4</sub> O <sub>2</sub> ·HCl·H <sub>2</sub> O			
Calculated (%)	C:66.07	H: 6.53	N:11.01
Found (%)	C:66.22	H: 6.42	N:10.99

20

Preparation Example 128

1-(5-Isopropyl-1-methyl-2-phenylindol-3-ylcarbonyl)-4-(2-pyridyl)homopiperazine hydrochloride

25

[0218] Melting point: 149-153°C

Elemental analysis for C <sub>29</sub> H <sub>32</sub> N <sub>4</sub> O·HCl·0.5H <sub>2</sub> O			
Calculated (%)	C:69.93	H: 6.88	N:11.25
Found (%)	C:69.98	H: 6.89	N:10.91

30

Preparation Example 129

35

1-(1,5-Dimethyl-2-phenylindol-3-ylcarbonyl)-4-(5-nitro-2-pyridyl)homopiperazine

40

[0219] Melting point: 228-229°C

Elemental analysis for C <sub>27</sub> H <sub>27</sub> N <sub>5</sub> O <sub>3</sub> ·0.25H <sub>2</sub> O			
Calculated (%)	C:68.41	H: 5.84	N:14.77
Found (%)	C:68.38	H: 5.92	N:14.57

45

Preparation Example 130

50

1-(1,5-Dimethyl-2-phenylindol-3-ylcarbonyl)-4-(5-methylpyridyl-2-yl)homopiperazine

[0220] Melting point: 148-150°C

Elemental analysis for C <sub>28</sub> H <sub>30</sub> N <sub>4</sub> O			
Calculated (%)	C:76.68	H: 6.89	N:12.77
Found (%)	C:76.73	H: 6.99	N:12.79

55

EP 1 243 268 A1

Preparation Example 131

1-[1,5-Dimethyl-2-(4-hydroxyphenyl)indol-3-ylcarbonyl]-4-(2-pyridyl)homopiperazine

5 [0221] Melting point: 265-266°C

10

Elemental analysis for C <sub>27</sub> H <sub>28</sub> N <sub>4</sub> O <sub>2</sub>			
Calculated (%)	C:73.61	H: 6.41	N:12.72
Found (%)	C:73.43	H: 6.57	N:12.58

Preparation Example 132

1-[1,5-Dimethyl-2-(4-methoxyphenyl)indol-3-ylcarbonyl]-4-(2-pyridyl)homopiperazine

15

[0222] Melting point: 159-160°C.

20

Elemental analysis for C <sub>28</sub> H <sub>30</sub> N <sub>4</sub> O <sub>2</sub>			
Calculated (%)	C:73.98	H: 6.65	N:12.33
Found (%)	C:74.14	H: 6.81	N:12.27

Preparation Example 133

25 1-(1,5-Dimethyl-2-phenylindol-3-ylcarbonyl)-4-(5-hydroxy-2-pyridyl)piperazine

[0223] Melting point: 256°C

30

Elemental analysis for C <sub>26</sub> H <sub>26</sub> N <sub>4</sub> O <sub>2</sub>			
Calculated (%)	C:73.22	H: 6.14	N:13.14
Found (%)	C:73.03	H: 6.20	N:13.20

Preparation Example 134

35 1-(1,5-Dimethyl-2-phenylindol-3-ylcarbonyl)-4-(5-hydroxy-2-pyridyl)homopiperazine

[0224] Melting point: 242°C

40

Elemental analysis for C <sub>27</sub> H <sub>28</sub> N <sub>4</sub> O <sub>2</sub>			
Calculated (%)	C:73.61	H: 6.41	N:12.72
Found (%)	C:73.53	H: 6.52	N:12.54

45

Preparation Example 135

1-(6-Chlorobenzothiazol-2-yl)-4-(1,5-dimethyl-2-phenylindol-3-ylcarbonyl)homopiperazine

50

[0225] Melting point: 177-179°C

Elemental analysis for C <sub>29</sub> H <sub>27</sub> ClN <sub>4</sub> OS			
Calculated (%)	C:67.62	H: 5.28	N:10.88
Found (%)	C:67.70	H: 5.53	N:10.81

55

## Preparation Example 136

1-(1,5-Dimethyl-2-phenylindol-3-ylcarbonyl)-4-(5-propyl-2-pyrimidinyl)homopiperazine

5 [0226] Melting point: 148-149°C

10

Elemental analysis for C <sub>29</sub> H <sub>33</sub> N <sub>5</sub> O			
Calculated (%)	C:74.49	H: 7.11	N:14.98
Found (%)	C:74.26	H: 7.25	N:14.85

## Preparation Example 137

1-(1,5-Dimethyl-2-phenylindol-3-ylcarbonyl)-4-(4-trifluoromethyl-2-pyrimidinyl)homopiperazine

15

[0227] Melting point: 155-157°C

20

Elemental analysis for C <sub>27</sub> H <sub>26</sub> F <sub>3</sub> N <sub>5</sub> O			
Calculated (%)	C:65.71	H: 5.31	N:14.19
Found (%)	C:65.89	H: 5.47	N:14.02

## Preparation Example 138

25 1-(1-Benzyl-5-methyl-2-phenylindol-3-ylcarbonyl)-4-(2-pyridyl)homopiperazine

[0228] Melting point: 163-164°C

30

Elemental analysis for C <sub>33</sub> H <sub>32</sub> N <sub>4</sub> O			
Calculated (%)	C:79.17	H: 6.44	N:11.19
Found (%)	C:78.80	H: 6.56	N:10.87

## Preparation Example 139

35 1-(5-Methyl-2-phenylindol-3-ylcarbonyl)-4-(2-pyridyl)homopiperazine

[0229] Melting point: 242-243°C

40

Elemental analysis for C <sub>26</sub> H <sub>26</sub> N <sub>4</sub> O			
Calculated (%)	C:76.07	H: 6.38	N:13.65
Found (%)	C:75.88	H: 6.49	N:13.46

45

## Preparation Example 140

1-(1-Carboxymethyl-5-methyl-2-phenylindol-3-ylcarbonyl)-4-(2-pyridyl)homopiperazine

50

[0230] Melting point: 198-204°C

Elemental analysis for C <sub>28</sub> H <sub>28</sub> N <sub>4</sub> O <sub>3</sub> ·0.25H <sub>2</sub> O			
Calculated (%)	C:71.09	H: 6.07	N:11.84
Found (%)	C:71.12	H: 6.14	N:11.96

55

EP 1 243 268 A1

Preparation Example 141

1-[1-(2-Hydroxyethyl)-5-methyl-2-phenylindol-3-ylcarbonyl]-4-(2-pyridyl)homopiperazine

5 [0231] Melting point: 127-130°C

Elemental analysis for C <sub>28</sub> H <sub>30</sub> N <sub>4</sub> O <sub>2</sub>			
Calculated (%)	C:73.98	H: 6.65	N:12.33
Found (%)	C:74.04	H: 6.84	N:12.58

10

Preparation Example 142

1-(1-Methyl-2-(2-methoxyphenyl)indol-3-ylcarbonyl)-4-(2-pyridyl)homopiperazine hydrochloride

15

[0232] Melting point: 156-160°C

Elemental analysis for C <sub>27</sub> H <sub>28</sub> N <sub>4</sub> O <sub>2</sub> ·HCl·0.75H <sub>2</sub> O			
Calculated (%)	C:66.11	H: 6.27	N:11.42
Found (%)	C:66.11	H: 6.69	N:11.48

20

Preparation Example 143

1-(1,5-Dimethyl-2-phenylindol-3-ylcarbonyl)-4-(5-methoxy-2-pyridyl)homopiperazine

25

[0233] Melting point: 124-126°C

Elemental analysis for C <sub>28</sub> H <sub>30</sub> N <sub>4</sub> O <sub>2</sub>			
Calculated (%)	C:73.98	H: 6.65	N:12.33
Found (%)	C:74.15	H: 6.76	N:12.39

30

Preparation Example 144

2-[4-(1,5-Dimethyl-2-phenylindol-3-ylcarbonyl)homopiperazin-1-yl]pyridine-5-carboxamide

35

[0234] Melting point: 186-188°C

Elemental analysis for C <sub>28</sub> H <sub>29</sub> N <sub>5</sub> O <sub>2</sub>			
Calculated (%)	C:69.26	H: 6.43	N:14.42
Found (%)	C:69.58	H: 6.29	N:14.44

40

Preparation Example 145

1-[1-Methyl-2-(2-pyridyl)indol-3-ylcarbonyl]-4-(2-pyridyl)homopiperazine

45

[0235] Melting point: 132-134°C

Elemental analysis for C <sub>25</sub> H <sub>25</sub> N <sub>5</sub> O			
Calculated (%)	C:72.97	H: 6.12	N:17.02
Found (%)	C:73.00	H: 6.19	N:16.88

50

EP 1 243 268 A1

Preparation Example 146

1-[1-Methyl-2-(4-pyridyl)indol-3-ylcarbonyl]-4-(2-pyridyl)homopiperazine

5 [0236] Melting point: 201-202°C

Elemental analysis for C <sub>25</sub> H <sub>25</sub> N <sub>5</sub> O				
Calculated (%)	C:72.97	H: 6.12	N:17.02	
Found (%)	C:72.87	H: 6.27	N:16.82	

10

Preparation Example 147

1-[5-Methyl-2-(3-methoxyphenyl)indol-3-ylcarbonyl]-4-(2-pyridyl)homopiperazine

15

[0237] Melting point: 112-115°C

Elemental analysis for C <sub>27</sub> H <sub>28</sub> N <sub>4</sub> O <sub>2</sub>				
Calculated (%)	C:73.61	H: 6.41	N:12.72	
Found (%)	C:73.12	H: 6.42	N:12.43	

20

Preparation Example 148

25

1-[5-Methyl-2-(2-methylphenyl)indol-3-ylcarbonyl]-4-(2-pyridyl)homopiperazine

[0238] Melting point: 243-245°C

Elemental analysis for C <sub>27</sub> H <sub>28</sub> N <sub>4</sub> O				
Calculated (%)	C:76.39	H: 6.65	N:13.20	
Found (%)	C:76.25	H: 6.64	N:12.95	

30

Preparation Example 149

35

1-[2-(2-Chlorophenyl)-5-methylindol-3-ylcarbonyl]-4-(2-pyridyl)homopiperazine

[0239] Melting point: 237-238°C

40

Elemental analysis for C <sub>26</sub> H <sub>25</sub> ClN <sub>4</sub> O				
Calculated (%)	C:70.18	H: 5.68	N:12.59	
Found (%)	C:69.81	H: 5.69	N:12.40	

45

Preparation Example 150

1-[2-(3-Chlorophenyl)-5-methylindol-3-ylcarbonyl]-4-(2-pyridyl)homopiperazine

50

[0240] Melting point: 241-244°C

Elemental analysis for C <sub>26</sub> H <sub>25</sub> ClN <sub>4</sub> O-0.4H <sub>2</sub> O				
Calculated (%)	C:69.06	H: 5.75	N:12.39	
Found (%)	C:69.27	H: 5.53	N:12.36	

55

EP 1 243 268 A1

Preparation Example 151

1-[1,5-Dimethyl-2-(3-methoxyphenyl)indol-3-ylcarbonyl]-4-(2-pyridyl)homopiperazine

5 [0241] Melting point: 90-93°C

10

Elemental analysis for C <sub>28</sub> H <sub>30</sub> N <sub>4</sub> O <sub>2</sub> ·0.25H <sub>2</sub> O			
Calculated (%)	C:73.26	H: 6.70	N:12.20
Found (%)	C:73.16	H: 6.80	N:12.00

Preparation Example 152

1-[1,5-Dimethyl-2-(2-methylphenyl)indol-3-ylcarbonyl]-4-(2-pyridyl) homopiperazine

15

[0242] Melting point: 90-96°C

20

Elemental analysis for C <sub>28</sub> H <sub>30</sub> N <sub>4</sub> O·0.25H <sub>2</sub> O			
Calculated (%)	C:75.90	H: 6.94	N:12.64
Found (%)	C:75.86	H: 7.03	N:12.43

Preparation Example 153

25 1-[2-(2-Chlorophenyl-1,5-dimethylindol-3-ylcarbonyl]-4-(2-pyridyl)homopiperazine

30

[0243] Melting point: 98-105°C

Elemental analysis for C <sub>27</sub> H <sub>27</sub> ClN <sub>4</sub> O·0.25H <sub>2</sub> O			
Calculated (%)	C:69.97	H: 5.98	N:12.09
Found (%)	C:70.12	H: 6.00	N:11.94

Preparation Example 154

35

1-[2-(3-Chlorophenyl-1,5-dimethylindol-3-ylcarbonyl]-4-(2-pyridyl)homopiperazine

[0244] Melting point: 101-104°C

40

Elemental analysis for C <sub>27</sub> H <sub>27</sub> ClN <sub>4</sub> O·0.25H <sub>2</sub> O			
Calculated (%)	C:69.97	H: 5.98	N:12.09
Found (%)	C:69.83	H: 5.97	N:11.93

45

Preparation Example 155

46

1-[4-(1,5-Dimethyl-2-phenylindol-3-ylcarbonyl)homopiperazin-1-yl]pyridine-5-carboxylic acid

[0245] Melting point: 259°C

50

Elemental analysis for C <sub>28</sub> H <sub>28</sub> N <sub>4</sub> O <sub>3</sub>			
Calculated (%)	C:71.78	H: 6.02	N:11.96
Found (%)	C:71.69	H: 6.14	N:11.95

55

EP 1 243 268 A1

Preparation Example 156

1-(1-Methyl-2-phenylindol-3-ylcarbonyl)-4-(5-nitro-2-pyridyl)homopiperazine

5 [0246] Melting point: 249-251°C

10

Elemental analysis for C <sub>26</sub> H <sub>25</sub> N <sub>5</sub> O <sub>3</sub> ·H <sub>2</sub> O			
Calculated (%)	C:65.95	H: 5.57	N:14.79
Found (%)	C:65.94	H: 5.42,	N:14.68

Preparation Example 157

1-(1-Ethyl-5-methyl-2-phenylindol-3-ylcarbonyl)-4-(5-nitro-2-pyridyl)homopiperazine

15

[0247] Melting point: 217-218°C

20

Elemental analysis for C <sub>28</sub> H <sub>29</sub> N <sub>5</sub> O <sub>3</sub> ·0.5H <sub>2</sub> O			
Calculated (%)	C:68.28	H: 6.14	N:14.22
Found (%)	C:68.47	H: 6.04	N:13.96

Preparation Example 158

25

1-(1,5-Dimethyl-2-phenylindol-3-ylcarbonyl)-4-(3-nitro-2-pyridyl)homopiperazine

[0248] Melting point: 184°C

30

Elemental analysis for C <sub>27</sub> H <sub>27</sub> N <sub>5</sub> O <sub>3</sub>			
Calculated (%)	C:69.07	H: 5.80	N:14.92
Found (%)	C:68.72	H: 5.89	N:14.79

Preparation Example 159

35

1-(1-Methyl-5-methoxy-2-phenylindol-3-ylcarbonyl)-4-(5-nitro-2-pyridyl)-homopiperazine

[0249] Melting point: 205°C

40

Elemental analysis for C <sub>27</sub> H <sub>27</sub> N <sub>5</sub> O <sub>4</sub>			
Calculated (%)	C:66.79	H: 5.60	N:14.42
Found (%)	C:66.48	H: 5.69	N:14.17

45

Preparation Example 160

50

1-(5-Fluoro-1-methyl-2-phenylindol-3-ylcarbonyl)-4-(5-nitro-2-pyridyl)homopiperazine

[0250] Melting point: 249°C

55

Elemental analysis for C <sub>26</sub> H <sub>24</sub> FN <sub>5</sub> O <sub>3</sub> ·H <sub>2</sub> O			
Calculated (%)	C:63.53	H: 5.33	N:14.25
Found (%)	C:63.66	H: 5.02	N:14.15

EP 1 243 268 A1

Preparation Example 161

1-(5-Bromo-1-methyl-2-phenylindol-3-ylcarbonyl)-4-(5-nitro-2-pyridyl)homopiperazine

5 [0251] Melting point: 242°C

Elemental analysis for C <sub>26</sub> H <sub>24</sub> BrN <sub>5</sub> O <sub>3</sub> ·0.5H <sub>2</sub> O			
Calculated (%)	C:57.47	H: 4.64	N:12.89
Found (%)	C:57.48	H: 4.45	N:12.72

10

Preparation Example 162

1-(1,6-Dimethyl-2-phenylindol-3-ylcarbonyl)-4-(5-nitro-2-pyridyl)homopiperazine

15 [0252] Melting point: 188°C

Elemental analysis for C <sub>27</sub> H <sub>27</sub> N <sub>5</sub> O <sub>3</sub>			
Calculated (%)	C:69.07	H: 5.80	N:14.92
Found (%)	C:69.01	H: 5.78	N:14.82

20

Preparation Example 163

25 1-(6-Chloro-1-methyl-2-phenylindol-3-ylcarbonyl)-4-(5-nitro-2-pyridyl)homopiperazine

[0253] Melting point: 199°C

30

Elemental analysis for C <sub>26</sub> H <sub>24</sub> ClN <sub>5</sub> O <sub>3</sub>			
Calculated (%)	C:63.74	H: 4.94	N:14.29
Found (%)	C:63.28	H: 4.84	N:14.14

Preparation Example 164

35

1-(4-Chloro-1-methyl-2-phenylindol-3-ylcarbonyl)-4-(5-nitro-2-pyridyl)homopiperazine

[0254] Melting point: 139°C

40

Elemental analysis for C <sub>26</sub> H <sub>24</sub> ClN <sub>5</sub> O <sub>3</sub>			
Calculated (%)	C:63.74	H: 4.94	N:14.29
Found (%)	C:63.94	H: 5.14	N:13.95

45

Preparation Example 165

1-(4-Bromo-1-methyl-2-phenylindol-3-ylcarbonyl)-4-(5-nitro-2-pyridyl)homopiperazine

[0255] Melting point: 160°C

50

Elemental analysis for C <sub>26</sub> H <sub>24</sub> BrN <sub>5</sub> O <sub>3</sub>			
Calculated (%)	C:58.44	H: 4.53	N:13.10
Found (%)	C:58.76	H: 4.69	N:12.72

55

**EP 1 243 268 A1**

Preparation Example 166

1-(6-Bromo-1-methyl-2-phenylindol-3-ylcarbonyl)-4-(5-nitro-2-pyridyl)homopiperazine

5 [0256] Melting point: 204°C

Elemental analysis for C <sub>26</sub> H <sub>24</sub> BrN <sub>5</sub> O <sub>3</sub> ·0.5H <sub>2</sub> O			
Calculated (%)	C:57.47	H: 4.64	N:12.89
Found (%)	C:57.67	H: 4.57	N:12.79

Preparation Example 167

1-(7-Bromo-1-methyl-2-phenylindol-3-ylcarbonyl)-4-(5-nitro-2-pyridyl) homopiperazine

15 [0257] Melting point: 252°C

Elemental analysis for C <sub>26</sub> H <sub>24</sub> BrN <sub>5</sub> O <sub>3</sub> ·0.5H <sub>2</sub> O			
Calculated (%)	C:57.47	H: 4.64	N:12.89
Found (%)	C:57.54	H: 4.57	N:12.73

Preparation Example 168

25 1-(6-Methoxy-1-methyl-2-phenylindol-3-ylcarbonyl)-4-(5-nitro-2-pyridyl)-homopiperazine

[0258] Melting point: 173°C

Elemental analysis for C <sub>27</sub> H <sub>27</sub> N <sub>5</sub> O <sub>4</sub>			
Calculated (%)	C:66.79	H: 5.60	N:14.42
Found (%)	C:66.31	H: 5.69	N:14.16

Preparation Example 169

35 1-(1,7-Dimethyl-2-phenylindol-3-ylcarbonyl)-4-(5-nitro-2-pyridyl)-homopiperazine

[0259] Melting point: 239°C

Elemental analysis for C <sub>27</sub> H <sub>27</sub> N <sub>5</sub> O <sub>3</sub> ·0.5H <sub>2</sub> O			
Calculated (%)	C:67.77	H: 5.90	N:14.63
Found (%)	C:67.53	H: 5.79	N:14.48

45 Preparation Example 170

1-(1-Ethyl-2-phenylindol-3-ylcarbonyl)-4-(5-nitro-2-pyridyl)-homopiperazine

[0260] Melting point: 264°C

Elemental analysis for C <sub>27</sub> H <sub>27</sub> N <sub>5</sub> O <sub>3</sub> ·0.9H <sub>2</sub> O			
Calculated (%)	C:66.76	H: 5.98	N:14.42
Found (%)	C:67.00	H: 5.79	N:14.39

55

EP 1 243 268 A1

Preparation Example 171

1-(1-Isopropyl-2-phenylindol-3-ylcarbonyl)-4-(5-nitro-2-pyridyl)-homopiperazine

5 [0261] Melting point: 271°C

Elemental analysis for C <sub>26</sub> H <sub>29</sub> N <sub>5</sub> O <sub>3</sub> ·0.2H <sub>2</sub> O			
Calculated (%)	C:69.03	H: 6.08	N:14.38
Found (%)	C:69.11	H: 6.17	N:14.51

10

Preparation Example 172

1-(7-Fluoro-1-methyl-2-phenylindol-3-ylcarbonyl)-4-(5-nitro-2-pyridyl)-homopiperazine

15 [0262] Melting point: 234°C

Elemental analysis for C <sub>26</sub> H <sub>24</sub> FN <sub>5</sub> O <sub>3</sub> ·0.7H <sub>2</sub> O			
Calculated (%)	C:64.24	H: 5.27	N:14.41
Found (%)	C:64.06	H: 5.14	N:14.27

20

Preparation Example 173

25 1-(7-Methoxy-1-methyl-2-phenylindol-3-ylcarbonyl)-4-(5-nitro-2-pyridyl)homopiperazine

[0263] Melting point: 178°C

Elemental analysis for C <sub>27</sub> H <sub>27</sub> N <sub>5</sub> O <sub>4</sub>			
Calculated (%)	C:66.79	H: 5.61	N:14.42
Found (%)	C:66.70	H: 5.56	N:14.38

30

Preparation Example 174

35 1-(1,5-Dimethyl-2-phenylindol-3-ylcarbonyl)-4-(5-methane-sulfonylamino-2-pyridyl)homopiperazine

[0264] Melting point: 215°C

Elemental analysis for C <sub>28</sub> H <sub>31</sub> N <sub>5</sub> O <sub>3</sub> S·0.25H <sub>2</sub> O			
Calculated (%)	C:64.41	H: 6.08	N:13.41
Found (%)	C:64.60	H: 6.14	N:13.09

40

45 Preparation Example 175

1-[1-Methyl-2-(4-pyridyl)indol-3-ylcarbonyl]-4-(5-nitro-2-pyridyl)homopiperazine

[0265] Melting point: 281°C

Elemental analysis for C <sub>25</sub> H <sub>24</sub> N <sub>6</sub> O <sub>3</sub> ·0.5H <sub>2</sub> O			
Calculated (%)	C:64.50	H: 5.41	N:18.05
Found (%)	C:64.32	H: 5.25	N:17.79

50

55

EP 1 243 268 A1

Preparation Example 176

1-[1-Methyl-2-(3-pyridyl)indol-3-ylcarbonyl]-4-(5-nitro-2-pyridyl)homopiperazine

5 [0266] Melting point: 229°C

10

Elemental analysis for C <sub>25</sub> H <sub>24</sub> N <sub>6</sub> O <sub>3</sub>			
Calculated (%)	C:65.78	H: 5.30	N:18.41
Found (%)	C:65.47	H: 5.47	N:18.54

Preparation Example 177

1-[1-Methyl-2-(2-pyridyl)indol-3-ylcarbonyl]-4-(5-nitro-2-pyridyl)homopiperazine

15

[0267] Melting point: 236°C

20

Elemental analysis for C <sub>25</sub> H <sub>24</sub> N <sub>6</sub> O <sub>3</sub> ·0.5H <sub>2</sub> O			
Calculated (%)	C:64.50	H: 5.41	N:18.05
Found (%)	C:64.65	H: 5.29	N:18.26

Preparation Example 178

25

1-(1,5-Dimethyl-2-phenylindol-3-ylcarbonyl)-4-(5-carbomethoxy-2-pyridyl)homopiperazine

[0268] Melting point: 202°C

30

Elemental analysis for C <sub>29</sub> H <sub>30</sub> N <sub>4</sub> O <sub>3</sub> ·0.2H <sub>2</sub> O			
Calculated (%)	C:71.64	H: 6.30	N:11.52
Found (%)	C:71.66	H: 6.24	N:11.48

Preparation Example 179

35

1-(5-Chloro-1-methyl-2-phenylindol-3-ylcarbonyl)-4-(5-nitro-2-pyridyl)homopiperazine

[0269] Melting point: 257°C

40

Elemental analysis for C <sub>26</sub> H <sub>24</sub> ClN <sub>5</sub> O <sub>3</sub> ·H <sub>2</sub> O			
Calculated (%)	C:61.48	H: 5.16	N:13.79
Found (%)	C:61.53	H: 4.80	N:13.71

45

Preparation Example 180

1-(1,5-Dimethyl-2-phenylindol-3-ylcarbonyl)-4-(5-acetylamino-2-pyridyl)homopiperazine

50

[0270] Melting point: 277°C

Elemental analysis for C <sub>29</sub> H <sub>31</sub> N <sub>5</sub> O <sub>2</sub> ·0.25H <sub>2</sub> O			
Calculated (%)	C:71.66	H: 6.53	N:14.41
Found (%)	C:71.90	H: 6.62	N:14.19

55

## Preparation Example 181

1-(1,5-Dimethyl-2-phenylindol-3-ylcarbonyl)-4-(5-dimethylamino-2-pyridyl)homopiperazine

5 [0271] Melting point: 178°C  
Positive ion EI-MS m/z: 467[M]<sup>+</sup>

## Preparation Example 182

1-(1,5-Dimethyl-2-phenylindol-3-ylcarbonyl)-4-(4-methyl-5-nitro-2-pyridyl)homopiperazine

10 [0272] Melting point: 222°C  
Positive ion EI-MS m/z: 483[M]<sup>+</sup>

## 15 Preparation Example 183

1-(1,5-Dimethyl-2-phenylindol-3-ylcarbonyl)-4-(5-diethylaminosulfonyl-2-pyridyl)homopiperazine

20 [0273] Melting point: 204°C  
IR (KBr) : 1587, 1333, 1161 cm<sup>-1</sup>

## Test example 1

Effect on anti-Thy-1 antibody nephritis in rats

25 [0274] Anti-Thy-1 antibody-induced nephritis is a model of glomerulonephritis constructed by utilizing the reaction between the Thy-1 antigen occurring as a membrane protein of mesangial cells and the antibody to the antigen. In this model, injuries to mesangial cells and lesions associated with mesangial cell proliferation are found. While a large majority of types of chronic glomerulonephritis in human are those of proliferative glomerulonephritis which show mesangial cell proliferation and increases in mesangial matrix as cardinal pathologic features, anti-Thy-1 antibody nephritis is regarded as a model of this human proliferative glomerulonephritis, particularly mesangial proliferative nephritis [Ishizaki et al., Acta. Pathol. Jpn., 36, 1191 (1986)].

## (1) Experimental animals

35 [0275] Rats were used in groups of 7.

## (2) Experimental materials

## 40 Preparation of anti-Thy-1 antibody

[0276] Preparation of the antibody was carried out in accordance with the method of Ishizaki et al. referred to above. Thus, an adjuvant suspension of rat thymocytes was prepared and subcutaneously administered to rabbits for immunization. After two booster doses, the blood was collected and the serum separated was subjected to inactivation and absorption to provide an antiserum (anti-Thy-1 antibody).

## (3) Experimental procedure

50 [0277] A predetermined amount of the antiserum was injected intravenously from the tail vein of rats to induce nephritis. Starting the following day after injection, a suspension (1mg/1ml) of the test drug was administered orally at a dosage of 1 ml/100g of body weight of rat twice a day for 7 days. On day 8 following the beginning of administration, the animals were sacrificed and the kidneys were removed. The kidney was fixed in Carnoy's fixative and, in the routine manner, paraffin sections were prepared and stained with hematoxyline stain for microscopy. For histopathological evaluation, the number of cells in the glomeruli (mainly mesangial cells) in each tissue preparation was counted under a light microscope. Statistical analysis was performed by Dunnett's test.

The results are shown in Table 1.

Table 1

Histopathological findings of glomeruli	
Test drug	Number of mesangial cells a)
Control	104.3±3.3
Preparation Compound No. 1	90.3±2.2*
Preparation Compound No.33	88.5±3.7**
Preparation Compound No.34	87.1±5.7**
Preparation Compound No.48	89.2±3.1*

a) Number of cells (mesangial cells) per glomerulus Mean ± standard error (the mean number of cells in the intact animal is 67.25)

\*: P<0.05, \*\*: P<0.01

[0278] It is clear from the above results that the compound of the present invention has inhibitory effect on mesangial cell proliferation in rats with anti-Thy-1 antibody nephritis.

#### Test Example 2

##### Acute toxicity

[0279] A suspension of the test drug was orally administered to mice at a dosage of 300 mg/kg, and their general condition was observed for a week after administration. Each of the compounds in Preparation Examples 1, 5, 6, 33, 34, 39, and 48 was administered. No deaths were observed in any of the administration groups.

Formulation Example 1	
Tablet (oral tablet)	
Formulation /tablet (in 80 mg)	
Compound of Preparation Example 1	5.0 mg
Corn Starch	46.6 mg
Crystalline cellulose	24.0 mg
Methyl cellulose	4.0 mg
Magnesium stearate	0.4 mg

[0280] The mixed powder at this ratio is compressed and molded to make oral tablets.

Formulation Example 2	
Tablet (oral tablet)	
Formulation /tablet (80 mg)	
Compound of Preparation Example 33	5.0 mg
Corn Starch	46.6 mg
Crystal cellulose	24.0 mg
Methyl cellulose	4.0 mg
Magnesium stearate	0.4 mg

[0281] The mixed powder at this ratio is compressed and molded to make oral tablets.

#### INDUSTRIAL APPLICABILITY

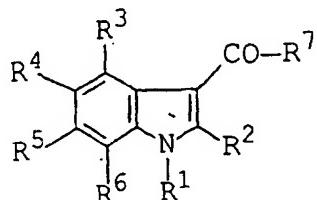
[0282] As shown above, since the compound of the invention has an excellent mesangial cell proliferation inhibitory activity and is a safe compound with low toxicity, a pharmaceutical composition containing the compound of the invention as an active ingredient is useful for the therapy of nephritis in mammals, including humans.

## Claims

1. A pharmaceutical composition for the therapy of nephritis which comprises an amide derivative represented by the following formula [1] or a pharmaceutically acceptable salt thereof, as an active ingredient:

5

10



15

[1]

wherein R<sup>1</sup> and R<sup>2</sup> may be the same or different and each is hydrogen, alkyl, haloalkyl, hydroxyalkyl, carboxyalkyl, acyl, aryl, aromatic heterocyclic group, or arylalkyl (the aryl moiety of the arylalkyl, the aryl and the aromatic heterocyclic group may be substituted by 1 to 3 same or different members selected from the group consisting of halogen, alkyl, haloalkyl, alkoxy, haloalkoxy, hydroxy, cyano, and nitro.);

R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup> and R<sup>6</sup> may be the same or different and each is hydrogen, halogen, hydroxy, amino, alkyl, haloalkyl, alkoxy, monoalkylamino, dialkylamino, arylalkyl, cyano or nitro. Or the two adjacent groups among R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup> and R<sup>6</sup> may jointly form methylenedioxy or ethylenedioxy;

R<sup>7</sup> represents cyclic amino which may be substituted by R<sup>8</sup>, or azabicycloalkylamino which may be substituted by R<sup>9</sup>;

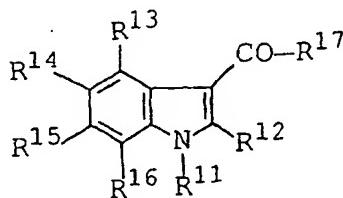
R<sup>8</sup> represents alkyl, haloalkyl, acyl, aryl, aromatic heterocyclic group or arylalkyl (the aryl moiety of the arylalkyl, the aryl and the aromatic heterocyclic group may be substituted by 1 to 3 same or different members selected from the group consisting of halogen, alkyl, arylalkyl, haloalkyl, alkoxy, hydroxy, amino, monoalkylamino, dialkylamino, alkylsulfonylamino, acylamino, dialkylaminosulfonylamino, carbamoyl, monoalkylcarbamoyl, dialkylcarbamoyl, cyano, carboxy, alkoxy carbonyl, alkylsulfonyl, dialkylaminosulfonyl and nitro.);

R<sup>9</sup> represents alkyl, alkenyl, (cycloalkyl)alkyl, haloalkyl, arylalkyl, acyl, alkylsulfonyl, or arylsulfonyl (the aryl moiety of the arylalkyl and the aryl moiety of the arylsulfonyl may be substituted by halogen or alkyl.).

- 35 2. A pharmaceutical composition for the therapy of nephritis which comprises an amide derivative represented by the following formula [1a] in either the following case (A) or (B), or a pharmaceutically acceptable salt thereof:

40

45



[1a]

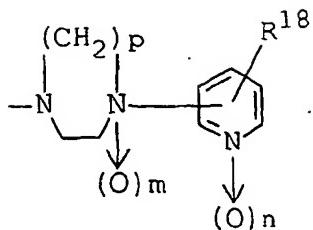
50

(A) wherein, R<sup>11</sup> and R<sup>12</sup> may be the same or different and each is alkyl, haloalkyl, hydroxyalkyl, carboxyalkyl, aryl, aromatic heterocyclic group, or arylalkyl (the aryl moiety of the arylalkyl, the aryl and the aromatic heterocyclic group may be substituted by 1 to 3 same or different members selected from the group consisting of halogen, alkyl, haloalkyl, alkoxy, haloalkoxy, hydroxy, cyano, and nitro.);

55

R<sup>13</sup>, R<sup>14</sup>, R<sup>15</sup> and R<sup>16</sup> may be the same or different and each is hydrogen, halogen, hydroxy, amino, alkyl, haloalkyl, alkoxy, monoalkylamino, dialkylamino, arylalkyl, cyano or nitro. Or the two adjacent groups among R<sup>13</sup>, R<sup>14</sup>, R<sup>15</sup> and R<sup>16</sup> may jointly form methylenedioxy or ethylenedioxy;

R<sup>17</sup> represents a group represented by the following formula [2]:



[2]

15 R<sup>18</sup> represents hydrogen, halogen, alkyl, arylalkyl, haloalkyl, alkoxy, hydroxy, amino, monoalkylamino, dialkylamino, alkylsulfonylamino, acylamino, dialkylaminosulfonylamino, carbamoyl, monoalkylcarbamoyl, di-alkylcarbamoyl, cyano, carboxy, alkoxy carbonyl, alkylsulfonyl, dialkylaminosulfonyl, or nitro; m represents 0 or 1; n represents 0 or 1; and p represents 2 or 3.

20 (B) wherein, R<sup>11</sup> represents hydrogen, alkyl, haloalkyl, hydroxyalkyl, carboxyalkyl, acyl, aryl, aromatic heterocyclic group or arylalkyl (the aryl moiety of the arylalkyl, the aryl and the aromatic heterocyclic group may be substituted by 1 to 3 same or different members selected from the group consisting of halogen, alkyl, haloalkyl, alkoxy, haloalkoxy, hydroxy, cyano and nitro.);

25 R<sup>12</sup> represents aryl or aromatic heterocyclic group (the aryl and the aromatic heterocyclic group may be substituted by 1 to 3 same or different members selected from the group consisting of halogen, alkyl, haloalkyl, alkoxy, hydroxy, cyano and nitro.);

30 R<sup>13</sup>, R<sup>14</sup>, R<sup>15</sup> and R<sup>16</sup> may be the same or different and each is hydrogen, halogen, hydroxy, amino, alkyl, haloalkyl, alkoxy, monoalkylamino, dialkylamino, arylalkyl, cyano or nitro. Or the two adjacent groups among R<sup>13</sup>, R<sup>14</sup>, R<sup>15</sup> and R<sup>16</sup> may jointly form methylenedioxy or ethylenedioxy;

35 R<sup>17</sup> represents a group represented by the following formula [3]:



[3]

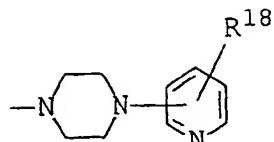
40 R<sup>19</sup> represents hydrogen, alkyl, alkenyl, (cycloalkyl)alkyl, haloalkyl, arylalkyl, acyl, alkylsulfonyl, or arylsulfonyl (the aryl moiety of the arylalkyl and the aryl moiety of the arylsulfonyl may be substituted by halogen or alkyl.).

45 3. The pharmaceutical composition for the therapy of nephritis according to Claim 2, which comprises an amide derivative or a pharmaceutically acceptable salt thereof as the active ingredient, R<sup>11</sup> is alkyl and R<sup>12</sup> is phenyl (the phenyl may be substituted by 1 to 3 same or different members selected from the group consisting of halogen, alkyl, haloalkyl, alkoxy, haloalkoxy, hydroxy, cyano, and nitro) in case (A).

50 4. The pharmaceutical composition for the therapy of nephritis according to Claim 2, which comprises an amide derivative or a pharmaceutically acceptable salt thereof as the active ingredient, wherein R<sup>11</sup> is alkyl and R<sup>12</sup> is phenyl (the phenyl may be substituted by 1 to 3 same or different members selected from the group consisting of halogen, alkyl, haloalkyl, alkoxy, haloalkoxy, hydroxy, cyano, and nitro) in case (B).

55 5. The pharmaceutical composition for the therapy of nephritis according to Claim 2, which comprises an amide derivative or a pharmaceutically acceptable salt thereof as the active ingredient, R<sup>11</sup> is alkyl and R<sup>12</sup> is phenyl, R<sup>13</sup>, R<sup>15</sup> and R<sup>16</sup> are respectively hydrogen, R<sup>14</sup> is hydrogen or alkyl, R<sup>17</sup> is a group represented by the following formula [2a]:

5



(2a)

10

R<sup>18</sup> is hydrogen or nitro in case (A).

- 15 6. The pharmaceutical composition for the therapy of nephritis which comprises an amide derivative selected from the group consisting of the following compounds (1) through (17) or a pharmaceutically acceptable salt thereof, as the active ingredient;

- 20 (1) 1-(1,5-Dimethyl-2-phenylindol-3-ylcarbonyl)-4-(2-pyridyl)piperazine  
 (2) 1-(1,5-Dimethyl-2-phenylindol-3-ylcarbonyl)-4-(3-pyridyl)piperazine  
 (3) 1-(1-Methyl-2-phenylindol-3-ylcarbonyl)-4-(5-nitro-2-pyridyl)piperazine  
 (4) 1-(1-Methyl-2-phenylindol-3-ylcarbonyl)-4-(2-pyridyl)piperazine-4-oxide  
 (5) 1-(1,5,6-Trimethyl-2-phenylindol-3-ylcarbonyl)-4-(4-pyridyl)piperazine  
 (6) 1-(1-Methyl-2-phenylindol-3-ylcarbonyl)-4-(2-pyridyl)piperazine  
 (7) 1-(1,5-Dimethyl-2-phenylindol-3-ylcarbonyl)-4-(4-pyridyl)piperazine  
 (8) 1-(1,5-Dimethyl-2-phenylindol-3-ylcarbonyl)-4-(5-nitro-2-pyridyl)piperazine  
 (9) 1-(1,5-Dimethyl-2-phenylindol-3-ylcarbonyl)-4-(2-pyridyl)homopiperazine  
 (10) 1-(1-Methyl-2-phenylindol-3-ylcarbonyl)-4-(3-pyridyl)homopiperazine  
 (11) 1-(1,5-Dimethyl-2-phenylindol-3-ylcarbonyl)-4-(3-pyridyl)homopiperazine  
 (12) 1-(1,5-Dimethyl-2-phenylindol-3-ylcarbonyl)-4-(5-nitro-2-pyridyl)homopiperazine  
 (13) 1-(1,5-Dimethyl-2-phenylindol-3-ylcarbonyl)-4-(5-methane-sulfonylamino-2-pyridyl)homopiperazine  
 (14) 1-(1,5-Dimethyl-2-phenylindol-3-ylcarbonyl)-4-(5-acetylamino-2-pyridyl)homopiperazine  
 (15) N-(endo-8-Methyl-8-azabicyclo[3.2.1]octa-3-yl)-1,5-dimethyl-2-phenylindole-3-carboxamide  
 (16) N-(endo-8-Methyl-8-azabicyclo[3.2.1]octa-3-yl)-5-methoxy-1-methyl-2-phenylindole-3-carboxamide and  
 (17) N-(endo-8-Methyl-8-azabicyclo[3.2.1]octa-3-yl)-1,6-dimethyl-2-phenylindole-3-carboxamide.

- 35 7. The pharmaceutical composition for the therapy of chronic glomerulonephritis which comprises an amide derivative or a pharmacologically acceptable salt thereof, which is defined in any of Claims 1 through 6, as an active ingredient.

- 40 8. The pharmaceutical composition for the therapy of proliferative glomerulonephritis which comprises an amide derivative or a pharmacologically acceptable salt thereof, which is defined in any of Claims 1 through 6, as an active ingredient.

45

50

55

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP00/08782

**A. CLASSIFICATION OF SUBJECT MATTER**  
 Int.Cl' A61K31/475, 496, 506, 551, A61P13/12 //  
 C07D401/12, 401/14, 409/14, 451/04, 491/056

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)  
 Int.Cl' A61K31/475, 496, 506, 551, A61P13/12,  
 C07D401/12, 401/14, 409/14, 451/04, 491/056

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)  
 CAPLUS, REGISTRY (STN)

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO, 96/32379, A1 (FUJISAWA PHARMACEUTICAL CO., LTD.), 17 January, 1996 (17.01.96), & CA, 2217707, A & AU, 9651234, A & EP, 820441, A1 & CN, 1187812, A & JP, 11-503445, A & ZA, 9602859, A & US, 6069156, A	1,2,7,8 3-6,9-15
X	JP, 10-67682, A (FUJISAWA PHARMACEUTICAL CO., LTD.), 10 March, 1998 (10.03.98) (Family: none)	1,2,7,8
PX	WO, 00/69432, A1 (TEIJIN LIMITED), 23 November, 2000 (23.11.00), Compound No. 749 (Family: none)	1,7,8
X	WO, 98/06715, A1 (SMITHKLINE BEECHAM CORP.), 19 February, 1998 (19.02.98), & EP, 922042, A1	1,7,8

 Further documents are listed in the continuation of Box C. See patent family annex.

## \* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"S" document member of the same patent family

Date of the actual completion of the international search  
19 February, 2001 (19.02.01)Date of mailing of the international search report  
27 February, 2001 (27.02.01)Name and mailing address of the ISA/  
Japanese Patent Office

Authorized officer

Facsimile No.

Telephone No.

THIS PAGE BLANK (USPTO)